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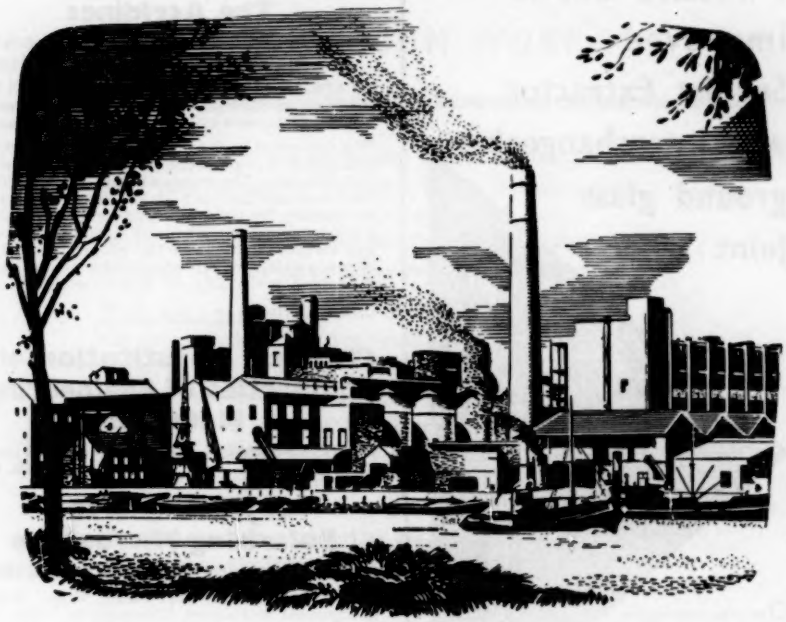

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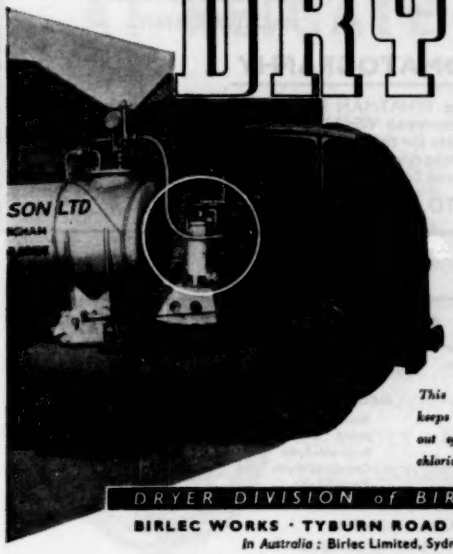

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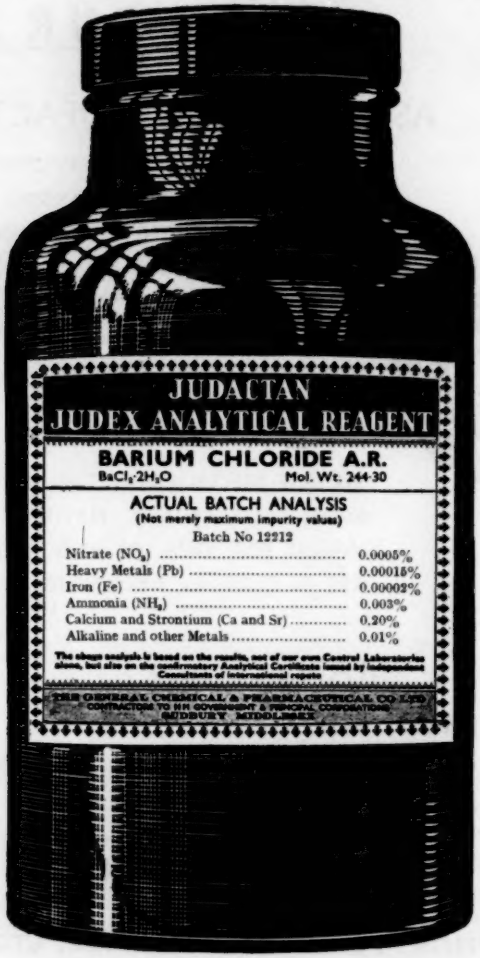
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By D. C. BRADLEY and W. WARDLAW 280

67. Organic Compounds of Platinum. Part I. The Preparation and Constitution of Trimethylplatinum Compounds.
By M. E. FOSS and (the late) C. S. GIBSON 299

69. The Hydrogen–Calomel Cell. Part I. The Hydrogen Electrode.
By G. J. HILLS and D. J. G. IVES 305

70. The Hydrogen–Calomel Cell. Part II. The Calomel Electrode.
By G. J. HILLS and D. J. G. IVES 311

71. The Hydrogen–Calomel Cell. Part III. The Standard E.M.F. at 25° C.
By G. J. HILLS and D. J. G. IVES 318

75. Reactions of the Cobaltic Ion. Part I. The Reaction of the Cobaltic Ion with Water.
By C. E. H. BAWN and A. G. WHITE 331

76. Reactions of the Cobaltic Ion. Part II. The Kinetics of the Reaction of the Cobaltic Ion with Formic Acid.
By C. E. H. BAWN and A. G. WHITE 339

77. Reactions of the Cobaltic Ion. Part III. The Kinetics of the Reactions of the Cobaltic Ion with Aldehydes and Alcohols.
By C. E. H. BAWN and A. G. WHITE 343

78. The Hydrolysis of Ferric Iron in Sulphate Solution.
By T. V. ARDEN 350

93. Magnetochemistry of the Heaviest Elements. Part III. The Halides of Ter- and Quadri-valent Uranium.
By J. K. DAWSON 429

101. Analysis of Inorganic Compounds by Paper Chromatography. Part I. Movement of Cations with Complex-forming Solvent Mixtures.
By F. H. POLLARD, J. F. W. MCOMIE, and I. I. M. ELBEIH 466

102. The Analysis of Inorganic Compounds by Paper Chromatography. Part II. Analysis of Cations and Anions.
By F. H. POLLARD, J. F. W. MCOMIE, and I. I. M. ELBEIH 470

105. Properties of Ion-exchange Resins in Relation to their Structure. Part II. Relative Affinities.
By D. REICHENBERG, K. W. PEPPER, and D. J. MCCAULEY 493

114. Substituted Benzidines and Related Compounds as Reagents in Analytical Chemistry. Part I. Solubilities of the Sulphates.
By R. BELCHER and A. J. NUTTEN 544

115. Substituted Benzidines and Related Compounds as Reagents in Analytical Chemistry. Part II. Reaction with Oxidising Agents.
By R. BELCHER and A. J. NUTTEN 546

116. Substituted Benzidines and Related Compounds as Reagents in Analytical Chemistry. Part III. 3-Methylbenzidine and 3 : 3′-Diethylbenzidine as Indicators in Argentometry.
By R. BELCHER and A. J. NUTTEN 547

117. Substituted Benzidines and Related Compounds as Reagents in Analytical Chemistry. Part IV. Naphthidine as Indicator in the Determination of Zinc with Ferrocyanide.
By R. BELCHER and A. J. NUTTEN 548

118. Substituted Benzidines and Related Compounds as Reagents in Analytical Chemistry. Part V. New Indicators for the Microvolumetric Determination of Gold.
By R. BELCHER and A. J. NUTTEN 550

128. The Kinetics of the Dissolution of Zinc in Aqueous Iodine Solutions. Part I.
By L. L. BIRCUMSHAW and A. C. RIDDIFORD 598

NOTES :

134. The Vapour Pressure of Diphenyl, Dibenzyl, and Diphenylmethane.
By NORMAN F. H. BRIGHT 624

Physical Organic.

PAGE

80. The Effect of Intramolecular Configuration on the Rate of Unimolecular Solvolysis of Aralkyl Chlorides.
By G. BADDELEY and J. CHADWICK 368

82. Alkyl–Oxygen Fission in Carboxylic Esters. Part VI. Solvolytic Reactions of Esters of Optically Active *cyclo*Hexylphenyl-, Methylphenyl-, and Methyl-α-naphthyl-carbinols.
By M. P. BALFE, G. H. BEAVEN, and J. KENYON 376

83. Alkyl–Oxygen Fission in Carboxylic Esters. Part VII. Hydrolysis of Methyl-β-naphthylcarbinyl Hydrogen Phthalate.
By M. P. BALFE, J. KENYON, and C. E. SEARLE 380

84. Alkyl–Oxygen Fission in Carboxylic Esters. Part VIII. Esters of *p*-Methylthio- and *p*-Methylsulphonyl-diphenylcarbinols.
By M. P. BALFE, R. E. DABBY, and J. KENYON 382

85. Alkyl–Oxygen Fission in Carboxylic Esters. Part IX. Methyl-2-thienylcarbinol.
By I. G. ANDERSON, M. P. BALFE, and J. KENYON 385

86. Alkyl–Oxygen Fission in Carboxylic Esters. Part X. Phthalates of Di-*p*-methoxyphenylcarbinol and of *tert.*-Alcohols.
By M. P. BALFE, J. KENYON, and E. M. THAIN 386

89. Chemical Actions of Ionising Radiations on Aqueous Solutions. Part VIII. Hydroxylation of Benzoic Acid by Free Radicals produced by *X*-Rays.
By (MISS) H. LOEBL, GABRIEL STEIN, and JOSEPH WEISS 405

95. Comparison of Weak Neutron Fluxes by Use of Organic Bromides.
By P. F. D. SHAW and C. H. COLLIE 434

96. Some (n, γ) Effects in Iodobenzene.
By P. F. D. SHAW 443

108. The Infra-red Spectrum of Tropolone.
By H. P. KOCH 512

Organic.

55. The 2-Phenylpyrrolines: A Redetermination of the Structures of the Supposed 2-Phenyl-Δ^3- and -Δ^4-pyrrolines.
By F. E. KING, J. R. MARSHALL, and P. SMITH 239

56. Syntheses from Phthalimido-acids. Part II. Further Reactions of Phthalylglutamic Anhydride.
By F. E. KING, B. S. JACKSON, and D. A. A. KIDD 243

57. The Synthesis of Pantothenic Acid-2′ and -4′ Phosphates as Possible Degradation Products of Coenzyme A.
By J. BADDILEY and E. M. THAIN 246

58. Thiophen Derivatives of Potential Biological Interest. Part II. Thionaphthen Analogues of Stilbene and Related Compounds.
By NG. PH. BUU-HOÏ and NG. HOÁN 251

59. Three New Analogues of Chloramphenicol.
By NG. PH. BUU-HOÏ, NG. D. XUONG, and NG. H. KHOÏ 255

60. Triterpenoids. Part I. Morolic Acid, a New Triterpenoid Sapogenin.
By D. H. R. BARTON and C. J. W. BROOKS 257

61. Triterpenoids. Part II. The Partial Synthesis of Morolic Acid.
By D. H. R. BARTON, C. J. W. BROOKS, and N. J. HOLNESS 278

63. Synthesis of Trehalose-type Disaccharides.
By VIOLET E. SHARP and M. STACEY 285

64. Cyclic Meso-ionic Compounds. Part IV. ψ-4-Aryl-2 : 4-dihydro-2-thio-1-thia-3 : 4-diazoles (" *endo*Thiodihydrothiodiazoles ").
By WILSON BAKER, W. D. OLLIS, A. PHILLIPS, and T. STRAWFORD 289

65. The Seed Fat of *Parinarium laurinum*. Part II. Component Glycerides of the Seed Fat.
By J. P. RILEY 291

66. Some Trinuclear Cyanine Dyes. Part IV. The Action of Acid on Dinuclear Intermediate Dyes.
By FRANCES M. HAMER 294

68. The Oxidation of Diphenylamine and of its *N*-Derivatives. Part II. Oxidation of the Benzyl Group of Some Benzylamines and Benzyl Ethers to Benzoyl.
By JAMES FORREST, S. HORWOOD TUCKER, and (MISS) MARGARET WHALLEY . 303

PAGE

72. Constitution of the Mucilage from the Bark of *Ulmus Fulva* (Slippery Elm Mucilage). Part III. The Isolation of 3-Monomethyl D-Galactose from the Products of Hydrolysis.
By E. L. HIRST, L. HOUGH, and J. K. N. JONES 323

73. The Action of Hydrazine on Benzoxazolones.
By J. D. BOWER and F. F. STEPHENS 325

74. An Investigation of the Reactions of Phenyl-lithium with Some Methylpyrimidines.
By T. D. HEYES and JOHN C. ROBERTS 328

79. Structure of an Antigenic Polysaccharide Isolated from Tuberculin.
By P. W. KENT 364

81. The (+)- and (−)-*o*-Tolyl-*p*-tolylcarbinols.
By M. P. BALFE, M. K. HARGREAVES, and J. KENYON 375

87. The Oxidation of Phenols with Benzoyl Peroxide. Part II.
By STANLEY L. COSGROVE and WILLIAM A. WATERS 388

88. Diamidides. Part I. Derivatives of Triazapentadiene and Tetra-azaheptatriene.
By F. C. COOPER, M. W. PARTRIDGE, and W. F. SHORT 391

90. Experiments relating to the Resolution of Tertiary Alcohols: the Resolution and Deamination of α-Naphthylphenyl-*p*-tolylmethylamine, and the Curtius, Hofmann, and Schmidt Reactions with 2-Methyl-2-phenylhexanoic Acid.
By C. L. ARCUS, J. KENYON, and S. LEVIN 407

91. The Preparation of 1-Substituted 1 : 2 : 3 : 4-Tetrahydrophosphinolines and 2-Substituted 1 : 2 : 3 : 4-Tetrahydro*iso*phosphinolines.
By M. H. BEEBY and FREDERICK G. MANN 411

92. Hentzsch's Isomeric Diazosulphonates.
By H. C. FREEMAN and R. J. W. LE FÈVRE 415

94. β-Aroylpropionic Acids. Part II. The Action of *o*- and *p*-Methoxyphenylmagnesium Bromide on Succinic Anhydride.
By F. G. BADDAR and LANSON S. EL-ASSAL 431

97. Syntheses of Structural Isomers of the Terpenes. Part I.
By G. R. CLEMO and B. K. DAVISON 447

98. The Chemistry of the Triterpenes. Part VII. An Inter-relationship between the Lupeol and the β-Amyrin Series. Elucidation of the Structure of Lupeol.
By T. R. AMES, T. G. HALSALL, and E. R. H. JONES 450

99. The Chemistry of the Triterpenes. Part VIII. The α- and β-Amyrenes.
By G. S. DAVY, T. G. HALSALL, and E. R. H. JONES 458

100. Experiments on the Preparation of Indolocarbazoles. Part III.
By P. V. CLIFTON and S. G. P. PLANT 461

103. Pteridine Studies. Part I. Pteridine, and 2- and 4-Amino- and 2- and 4-Hydroxy-pteridines.
By ADRIEN ALBERT, D. J. BROWN, and GORDON CHEESEMAN 474

104. Antituberculous Compounds. Part VII. Some Further *N*-Substituted Amidines and Analogues.
By P. T. CHARLTON, G. K. MALIPHANT, P. OXLEY, and D. A. PEAK 485

106. The Selective Absorption of Optical Antipodes by Proteins.
By WILLIAM BRADLEY and GERALD C. EASTY 499

107. Tropolones. Part I. The Preparation and General Characteristics of Tropolone.
By J. W. COOK, A. R. GIBB, R. A. RAPHAEL, and A. R. SOMERVILLE . . 503

109. Preliminary Syntheses in the Morphine Series. Part II. The Synthesis of 2-Aryl-*cyclo*hex-2-enones.
By DAVID GINSBURG and RAPHAEL PAPPO 516

110. Interaction of Alcohols with Silicon Tetrachloride.
By W. GERRARD and A. H. WOODHEAD 519

111. Acylation Reactions catalysed by Strong Acids. Part III. The Acetylium Ion as a Debenzylating Agent.
By H. BURTON and P. F. G. PRAILL 522

112. Acylation Reactions catalysed by Strong Acids. Part IV. "Benzoyl and Substituted Benzoyl Perchlorates" as *C*-Aroylating Agents.
By H. BURTON and P. F. G. PRAILL 529

113. Aneurin. Part X. The Mechanism of Thiochrome Formation from Aneurin and Aneurin Disulphide.
By P. SYKES and A. R. TODD 534

PAGE

119. New Syntheses of Heterocyclic Compounds. Part XII. The Condensation of Ethyl β-Aminocrotonate with Some Cyclic Amidines.
By H. ANTAKI and V. PETROW 551

120. *N*-(*N'*-Phenylacetylseryl)-D-penicillamines as Possible Biological Precursors of Benzylpenicillin.
By WILSON BAKER and W. D. OLLIS 556

121. Purpurogallin. Part IV. Some Properties of Tropolones.
By ROBERT D. HAWORTH and JOHN D. HOBSON 561

122. The Chemistry of Extractives from Hardwoods. Part IV. Okanin and *iso*Okanin, the Isomeric 2 : 3 : 4 : 3' : 4'-Pentahydroxychalkones.
By F. E. KING and T. J. KING 569

123. The Vapour-phase Oxidation of Methyl*cyclo*pentane.
By J. H. BURGOYNE and J. A. SILK 572

124. The Reactions of Metallic Salts of Acids with Halogens. Part I. The Reaction of Metal Trifluoroacetates with Iodine, Bromine, and Chlorine.
By R. N. HASZELDINE 584

125. The Reactions of Fluorocarbon Radicals. Part IV. The Synthesis of 3 : 3 : 3-Trifluoropropyne.
By R. N. HASZELDINE 588

126. Pteridines. Part II. The Synthesis of Some α-(5-Nitro-4-pyrimidylamino)-ketones and Their Conversion into 7 : 8-Dihydropteridines and Pteridines.
By W. R. BOON and W. G. M. JONES 591

127. The Enzymic Synthesis and Degradation of Starch. Part XII. The Mechanism of Synthesis of Amylopectin.
By P. N. HOBSON, W. J. WHELAN, and S. PEAT 596

129. Organic Fluorides. Part VI. The Chemical and Physical Properties of Certain Fluorocarbons.
By R. N. HASZELDINE and F. SMITH 603

130. Organic Fluorides. Part VII. Co-ordination Compounds of Fluoroacetylacetones.
By R. N. HASZELDINE, W. K. R. MUSGRAVE, F. SMITH, and (MISS) L. M. TURTON 609

131. Specification of Configuration about Quadricovalent Asymmetric Atoms.
By R. S. CAHN and C. K. INGOLD 612

NOTES :

132. The Formation of Osazones. Part II. The Formation of Glucosazone.
By G. J. BLOINK and K. H. PAUSACKER 622

133. The Determination of Phosphorus in Deoxypentose Nucleic Acids.
By A. S. JONES, W. A. LEE, and A. R. PEACOCKE 623

135. 3 : 6-Diamidinodibenzofuran.
By J. S. MOFFATT 625

136. Difficulties in the Alkylation of 2 : 6-Di-iodo-4-nitrophenol.
By J. H. WILKINSON 626

OBITUARY NOTICES :

CHARLES STANLEY GIBSON 628

DONALD CUMMING WILSON 637

INDEX OF AUTHORS' NAMES.

ALBERT, A., Brown, D. J., and Cheeseman, G., 474.
Ames, T. R., Halsall, T. G., and Jones, E. R. H., 450.
Anderson, I. G., Balfe, M. P., and Kenyon, J., 385.
Ankati, H., and Petrow, V., 551.
Arcus, C. L., Kenyon, J., and Levin, S., 407.
Arden, T. V., 350.
Baddar, F. G., and El-Assal, L. S., 431.
Baddeley, G., and Chadwick, J., 368.
Baddiley, J., and Thain, E. M., 246.
Baker, W., and Ollis, W. D., 556.
Baker, W., Ollis, W. D., Phillips, A., and Strawford, T., 289.
Balfe, M. P., Beaven, G. H., and Kenyon, J., 376.
Balfe, M. P., Dabby, R. E., and Kenyon, J., 382.
Balfe, M. P., Hargreaves, M. K., and Kenyon, J., 375.
Balfe, M. P., Kenyon, J., and Searle, C. E., 380.
Balfe, M. P., Kenyon, J., and Thain, E. M., 386.
Balfe, M. P. See also Anderson, I. G., 385.
Barton, D. H. R., and Brooks, C. J. W., 257.
Barton, D. H. R., Brooks, C. J. W., and Holness, N. J., 278.

Bawn, C. E. H., and White, A. G., 331, 339, 343.
Beaven, G. H. See Balfe, M. P., 376.
Beeby, M. H., and Mann, F. G., 411.
Belcher, R., and Nutten, A. J., 544, 546, 547, 548, 550.
Bircumshaw, L. L., and Riddiford, A. C., 598.
Bloink, G. J., and Pausacker, K. H., 622.
Boon, W. R., and Jones, W. G. M., 591.
Bower, J. D., and Stephens, F. F., 325.
Bradley, D. C., and Wardlaw, W., 280.
Bradley, W., and Easty, G. C., 499.
Bright, N. F. H., 624.
Brooks, C. J. W. See Barton, D. H. R., 257, 278.
Brown, D. J. See Albert, A., 474.
Burgoyne, J. H., and Silk, J. A., 572.
Burton, H., and Praill, P. F. G., 522, 529.
Buu-Hoï, Ng. Ph., and Hoán, Ng., 251.
Buu-Hoï, Ng. Ph., Xuong, Ng. D., and Khoï, Ng. H., 255.
Cahn, R. S., and Ingold, C. K., 612.
Chadwick, J. See Baddeley, G., 368.
Charlton, P. T., Maliphant, G. K., Oxley, P., and Peak, D. A., 485.
Cheeseman, G. See Albert, A., 474.
Clemo, G. R., and Davison, B. K., 447.
Clifton, P. V., and Plant, S. G. P., 461.
Collie, C. H. See Shaw, P. F. D., 434.
Cook, J. W., Gibb, A. R., Raphael, R. A., and Somerville, A. R., 503.
Cooper, F. C., Partridge, M. W., and Short, W. F., 391.
Cosgrove, S. L., and Waters, W. A., 388.
Dabby, R. E. See Balfe, M. P., 382.
Davison, B. K. See Clemo, G. R., 447.
Davy, G. S., Halsall, T. G., and Jones, E. R. H., 458.
Dawson, J. K., 429.
Easty, G. C. See Bradley, W., 499.
El-Assal, L. S. See Baddar, F. G., 431.
Elbeih, I. I. M. See Pollard, F. H., 466, 470.
Forrest, J., Tucker, S. H., and Whalley, M., 303.
Foss, M. E., and Gibson, C. S., 299.
Freeman, H. C., and Le Fèvre, R. J. W., 415.
Gerrard, W., and Woodhead, A. H., 519.
Gibb, A. R. See Cook, J. W., 503.
Gibson, C. S. See Foss, M. E., 299.
Ginsburg, D., and Pappo, R., 516.
Halsall, T. G. See Ames, T. R., 450, and Davy, G. S., 458.
Hamer, F. M., 294.
Hargreaves, M. K. See Balfe, M. P., 375.
Haszeldine, R. N., 584, 588.
Haszeldine, R. N., Musgrave, W. K. R., Smith, F., and Turton, L. M., 609.
Haszeldine, R. N., and Smith, F., 603.
Haworth, R. D., and Hobson, J. D., 561.
Heyes, T. D., and Roberts, J. C., 328.
Hills, G. J., and Ives, D. J. G., 305, 311, 318.
Hirst, E. L., Hough, L., and Jones, J. K. N., 323.
Hoán, Ng. See Buu-Hoï, Ng. Ph., 251.
Hobson, J. D. See Haworth, R. D., 561.
Hobson, P. N., Whelan, W. J., and Peat, S., 596.
Holness, N. J. See Barton, D. H. R., 278.
Hough, L. See Hirst, E. L., 323.
Ingold, C. K. See Cahn, R. S., 612.
Ives, D. J. G. See Hills, G. J., 305, 311, 318.
Jackson, B. S. See King, F. E., 243.
Jones, A. S., Lee, W. A., and Peacocke, A. R., 623.
Jones, E. H. R. See Ames, T. R., 450, and Davy, G. S., 458.
Jones, J. K. N. See Hirst, E. L., 323.
Jones, W. G. M. See Boon, W. R., 591.
Kent, P. W., 364.
Kenyon, J. See Anderson, I. G., 385, Arcus, C. L., 407, and Balfe, M. P., 375, 376, 380, 382, 386.
Khoï, Ng. H. See Buu-Hoï, Ng. Ph., 255.
Kidd, D. A. A. See King, F. E., 243.
King, F. E., Jackson, B. S., and Kidd, D. A. A., 243.
King, F. E., and King, T. J., 569.
King, F. E., Marshall, J. R., and Smith, P., 239.
King, T. J. See King, F. E., 569.
Koch, H. P., 512.
Lee, W. A. See Jones, A. S., 623.
Le Fèvre, R. J. W. See Freeman, H. C., 415.
Levin, S. See Arcus, C. L., 407.
Loebl, H., Stein, G., and Weiss, J., 405.
McCauley, D. J. See Reichenberg, D., 493.
McOmie, J. F. W. See Pollard, F. H., 466, 470.
Maliphant, G. K. See Charlton, P. T., 485.
Mann, F. G. See Beeby, M. H., 411.
Marshall, J. R. See King, F. E., 239.
Moffatt, J. S., 625.
Musgrave, W. K. R. See Haszeldine, R. N., 609.
Nutten, A. J. See Belcher, R., 544, 546, 547, 548, 550.
Ollis, W. D. See Baker, W., 289, 556.
Oxley, P. See Charlton, P. T., 485.
Pappo, R. See Ginsburg, D., 516.
Partridge, M. W. See Cooper, F. C., 391.
Pausacker, K. H. See Bloink, G. J., 622.
Peacocke, A. R. See Jones, A. S., 623.
Peak, D. A. See Charlton, P. T., 485.
Peat, S. See Hobson, P. N., 596.
Pepper, K. W. See Reichenberg, D., 493.
Petrow, V. See Ankati, H., 551.
Phillips, A. See Baker, W., 289.
Plant, S. G. P. See Clifton, P. V., 461.
Pollard, F. H., McOmie, J. F. W., and Elbeih, I. I. M., 466, 470.
Praill, P. F. G. See Burton, H., 522, 529.
Raphael, R. A. See Cook, J. W., 503.
Reichenberg, D., Pepper, K. W., and McCauley, D. J., 493.
Riddiford, A. C. See Bircumshaw, L. L., 598.
Riley, J. P., 291.
Roberts, J. C. See Heyes, T. D., 328.
Searle, C. E. See Balfe, M. P., 380.
Sharp, V. E., and Stacey, M., 285.
Shaw, P. F. D., 443.
Shaw, P. F. D., and Collie, C. H., 434.
Short, W. F. See Cooper, F. C., 391.
Silk, J. A. See Burgoyne, J. H., 572.
Smith, F. See Haszeldine, R. N., 603, 609.
Smith, P. See King, F. E., 239.
Somerville, A. R. See Cook, J. W., 503.
Stacey, M. See Sharp, V. E., 285.
Stein, G. See Loebl, H., 405.
Stephens, F. F. See Bower, J. D., 325.
Strawford, T. See Baker, W., 289.
Sykes, P., and Todd, A. R., 534.
Thain, E. M. See Baddiley, J., 246, and Balfe, M. P., 386.
Todd, A. R. See Sykes, P., 534.
Tucker, S. H. See Forrest, J., 303.
Turton, L. M. See Haszeldine, R. N., 609.
Wardlaw, W. See Bradley, D. C., 280.
Waters, W. A. See Cosgrove, S. L., 388.
Weiss, J. See Loebl, H., 405.
Whalley, M. See Forrest, J., 303.
Whelan, W. J. See Hobson, P. N. 596.
White, A. G. See Bawn, C. E. H., 331, 339, 343.
Wilkinson, J. H., 626
Woodhead, A. H. See Gerrard, W., 519.
Xuong, Ng. D. See Buu-Hoï, Ng. Ph., 255.

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NOMENCLATURE. 11. Authors are expected to be familiar with the normal rules of nomenclature, but are invited to communicate with the Editor if in doubt or in special cases. Some of the principles followed in the *Journal* are reviewed in "Modern Chemical Nomenclature," by Dr. Clarence Smith (*J.*, 1936, 1067); reprints of this paper may be obtained by Fellows, price 2*d*. post free, from the General Secretary. Much valuable discussion will be found in "British Chemical Nomenclature," by Dr. A. D. Mitchell [Edward Arnold & Co., 1948]. Authors should choose their symbols from the "Report of a Joint Committee of the Chemical Society, Faraday Society, and the Physical Society on Symbols for Thermodynamical and Physico-Chemical Quantities and Conventions Relating to their Use," copies of which may be obtained by Fellows, price 4*d*. post free, from the General Secretary.

NEW COMPOUNDS. 12. New compounds should be indicated by underlining the name at its first mention (excluding headings) in the Experimental section *only*, and by giving analytical results in the form: "Found: ———. ——— requires ———." Analytical results for compounds which have previously been adequately described in the literature should be given in the form: "Found: ———. Calc. for ———: ———."

ILLUSTRATIONS. 13. Illustrations accompanying the papers must be carefully drawn, preferably *twice* the size of the finished block (max. width 5 inches), *in Indian ink, on good white cartridge paper* (graph paper with faint blue lines is acceptable). Any illustration which seriously exceeds four times the size of the finished block will be returned to the author for re-drawing to a smaller scale. Lettering on the drawings, whether on the margin or in the body of the drawing, must not be in ink but must be inserted *clearly but lightly in pencil*. *Margins* of at least two inches must be left. Authors may, if they wish, submit in the first place clearly drawn pencil sketches instead of the completed diagrams, which, however, must be supplied before publication. Further information can be obtained from the Editor.

PROOFS. 14. Authors will be expected to pay the cost of any considerable changes made by them in proof, apart from the correction of printers' errors. See also paragraph 7.

PREPRINTS. 15. Each author, or joint author, receives 10 preprints (without covers) free of charge. A quotation for extra preprints and an order form will be sent with the proofs. The order form (and any necessary remittance) must be returned with the proofs.

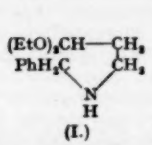
55. *The 2-Phenylpyrrolines: A Redetermination of the Structures of the Supposed 2-Phenyl-Δ³- and -Δ⁴-pyrrolines.*

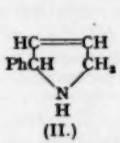
By F. E. King, J. R. Marshall, and P. Smith.

As already briefly reported (King, *J.*, 1949, 1318), the crystalline product resulting from the action of hydrochloric acid on ethyl 3-benzylaminopropionacetal (3-benzylamino-1 : 1-diethoxypropane) is a salt of 2 : 4 : 6-tri-(2-benzylaminoethyl)trioxan, the aldehyde trimer, and not 2-phenyl-Δ³-pyrroline hydrochloride (Wohl, *Ber.*, 1901, **34**, 1914). On the other hand, cyclisation to a pyrroline does apparently occur with the homologous butyracetal since its acid-hydrolysis product can be reduced to 1-benzylpyrrolidine.

The 2-phenylpyrroline prepared by Gitsels and Wibaut and believed by them to be the Δ⁴-pyrroline (*Rec. Trav. chim.*, 1941, **60**, 50), has been shown by oxidation to *N*-α-carboxybenzylglycine to be the Δ³-isomer. By analogy the dihydronicotyrine of Wibaut and Hackmann (*ibid.*, 1932, **51**, 1157), regarded by Späth, Wibaut, and Kesztler (*Ber.*, 1938, **71**, 100) as a Δ²-pyrroline, is very probably 2-3′-pyridyl-Δ³-pyrroline, a conclusion independently reached by Haines and Eisner (*J. Amer. Chem. Soc.*, 1950, **72**, 1719).

Wohl (*Ber.*, 1901, **34**, 1914; 1905, **38**, 4154) has shown that the action of acids on 3-amino-1 : 1-diethoxypropane and 1 : 1-diethoxy-3-ethylaminopropane (ethyl 3-amino- and 3-ethylaminopropionacetal) leads to the formation of salts of the aldehyde polymers, and analogous compounds were similarly obtained by Voet (*Bull. Soc. chim.*, 1929, **45**, 61) from other secondary amino- and from tertiary amino-propionacetals. The pure products possess only weak aldehydic properties, and from a cryoscopic determination of the molecular weight of the 3-ethylamino-base were believed to be three-fold polymers. The 3-benzylamino-acetal (I), however, appeared to be exceptional in giving with cold concentrated hydrochloric acid a salt which Wohl (*loc. cit.*, 1901) described as the hydrochloride of 2-phenyl-Δ³-pyrroline (II). Neither the free base nor any other derivative was prepared, and although the constitution of the compound has hitherto been accepted without comment (see Gitsels and Wibaut, *Rec. Trav. chim.*, 1941, **60**, 50; Murray and Cloke, *J. Amer. Chem. Soc.*, 1946, **68**, 126), the evidence for this unique synthesis of a Δ³-pyrroline seemed unconvincing, and the reaction has therefore been re-investigated.


(I.)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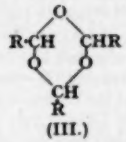

(III.)

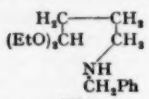
The required acetal (I) was prepared both by Wohl's method, *i.e.*, reduction of the benzylideneamino-acetal, and also from the 3-chloro-acetal by heating it with benzylamine. The identity of the products, which are liquid, was shown by their common crystalline picrolonate. On treatment with the appropriate reagents, the benzylamino-acetal rapidly formed the 2 : 4-dinitrophenylhydrazone hydrochloride and sulphate.

The composition attributed by Wohl to the product obtained from the acetal and hydrochloric acid rests on analyses of nitrogen and chlorine, but from more complete determinations which have now been made it is evident that the empirical formula of the salt is $C_{10}H_{13}ON,HCl$, and not $C_{10}H_{11}N,HCl$ as stated by Wohl. Intensive desiccation does not eliminate the additional elements H_2O, and analyses of the oxalate, sulphate, and picrolonate which were then prepared confirm that the elementary composition of the base is $C_{10}H_{13}ON$. The latter is, of course, the molecular formula of 3-benzylaminopropaldehyde but, although the free amine—a syrupy liquid obtained by shaking an aqueous solution of the hydrochloride with magnesium oxide under ether—resinified on attempted distillation, even under very low pressure, from its lack of reducing properties it was clearly not the simple aldehyde. However, when the amine hydrochloride was heated with the necessary reagent, 3-benzylaminopropaldehyde 2 : 4-dinitrophenylhydrazone hydrochloride was slowly formed, thus demonstrating Wohl's compound to be merely a polymer of the aldehyde. The degree of polymerisation was indicated by a determination of the molecular weight of the base in benzene. The first values obtained corresponded to rather

more than two units per molecule, but after the compound had been kept in a vacuum over phosphoric oxide for several days a steady figure indicative of the trimer, 2 : 4 : 6-tri-(2-benzylaminoethyl)trioxan (III; R = Ph·CH_2·NH·CH_2·CH_2·), was attained. The rising value of the molecular weight is thought to be caused by the slow removal of a small amount of water originally present; there is no evidence that when first liberated from its hydrochloride the product contains unassociated amino-aldehyde.

The formation of cyclic amines through intramolecular condensation of aldehyde and active methylene groups, though later successfully used by Wohl in the well-known synthesis of cincholoiponic acid (Wohl, *Ber.*, 1907, **40**, 4679; Wohl and Losanitsch, *ibid.*, p. 4698), therefore does not occur in the extreme case of benzylaminopropaldehyde, in which the activating effect of the phenyl group, already feeble, is probably opposed, even in acid solution, by the adjacent nitrogen atom. However, at an early stage in the investigation the presence of oxygen in the formula was tentatively attributed to a ring-closure of the type postulated by Wohl but without dehydration, thus giving 3-hydroxy-2-phenylpyrrolidine. In order to detect the possible hydroxyl group the amine hydrochloride was heated with acetic anhydride, whereupon hydrogen chloride was evolved and a high-boiling liquid, $C_{16}H_{21}O_3N$, isolated, which from its ready formation of a 2 : 4-dinitrophenylhydrazone was later recognised as 1 : 1-diacetoxy-3-*N*-benzylacetamidopropane (IV). The original 3-benzylamino-acetal, on the other hand, was converted under these conditions into 3-*N*-benzylacetamidoprop-1-enyl ethyl ether (V), which, of course, gave the same 2 : 4-dinitrophenylhydrazone.

(IV.) $PhCH_2$·NAc·CH_2·CH_2·$CH(OAc)_2$ $PhCH_2$·NAc·CH_2·CH:CH·OEt (V.)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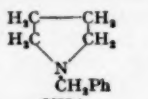
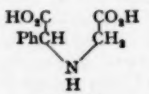

(VII.)


(VIII.)

As was to be expected, the effect of hydrochloric acid on the higher homologue, 4-benzylamino-1 : 1-diethoxybutane (ethyl 4-benzylaminobutyracetal) (VI), leads to intramolecular condensation of the liberated aldehyde group with the basic atom. The acid-cyclised base could not be isolated in a pure condition, although a picrolonate was obtained which may have been that of the pyrroline, but when the hydrochloric acid solution was heated with tin the nature of the initial reaction was apparent from the formation of 1-benzylpyrrolidine (VII) characterised by its picrate (Schlinck, *Ber.*, 1899, **32**, 953) and picrolonate. The benzylaminobutyracetal (VI) was synthesised by reduction of the benzylideneamino-compound. In connexion with intended synthetical experiments, the *N*-cyanomethyl compounds of both the 4-aminobutyracetal and (I) were prepared by the Strecker method.

The revision of the formula assigned by Wohl to the acid-hydrolysis product of (I) affects the argument used by Gitsels and Wibaut (*loc. cit.*) when proposing a structure for the 2-phenylpyrroline they obtained by zinc–acid reduction of 2-phenylpyrrole. The dihydro-base is readily methylated, from which these authors concluded that it was not a Δ^1- or a Δ^5-pyrroline; its stability to acid is, in any case, sufficient for us to reject these two structures. In view of the existence of the 2-phenyl-Δ^2-pyrroline (Gabriel and Colman, *Ber.*, 1908, **41**, 513), and also, apparently, of the Δ^3-isomer, Gitsels and Wibaut therefore considered their dihydropyrrole to be the Δ^4-compound.

With the elimination of Wohl's Δ^3-pyrroline other evidence is necessary to establish the constitution of the isomer prepared by Gitsels and Wibaut. The synthesis of the supposed Δ^4-pyrroline has accordingly been repeated; by reversing the published procedure, and slowly treating an ethanolic solution of 2-phenylpyrrole and zinc dust with acid, thus avoiding undue contact of the latter with the pyrrole, the yield of pyrroline has been considerably increased. The constitution of Δ^3-pyrroline, also obtained by zinc–acid reduction from pyrrole, was determined by ozonolysis (Treibs and Dinelli, *Annalen*, 1935, **517**, 170), the oxidation ultimately giving iminodiacetic acid, but Gitsels and Wibaut report that a similar attempt to oxidise their phenyldihydropyrrole was unsuccessful owing to extensive decomposition. The passage of ozone into an aqueous acid solution of the 2-phenylpyrroline, although at first causing the deposition of dark amorphous material, ultimately gave a nearly colourless solution. After further oxidation with hydrogen peroxide, and treatment with ethanolic hydrogen chloride, a liquid base was isolated which was identified by means of its hydrochloride, picrolonate, and the crystalline acid obtained on hydrolysis (all of which were indistinguishable from specimens

previously synthesised), as the diethyl ester of *N*-α-carboxybenzylglycine (VIII). The synthesis of *N*-α-carboxybenzylglycine was accomplished by the Strecker reaction from benzaldehyde, ethyl aminoacetate, and hydrogen cyanide (Stadnikoff, *Ber.*, 1908, **41**, 4364; Scheibler and Baumgarten, *ibid.*, 1922, **55**, 1358), the intermediate cyano-ester being hydrolysed with boiling hydrochloric acid. The ethyl ester was obtained from a previously heated solution of α-phenylglycine ethyl ester and chloroacetic acid by refluxing with hydrogen chloride, and, in addition to the derivatives mentioned above, the toluene-*p*-sulphonyl derivative was prepared.

In view of the evidence now available that 2-phenylpyrrole undergoes 1 : 4-hydrogenation on zinc–acid reduction, it is difficult to accept the conclusion that the 2-3′-pyridylpyrroline of Wibaut and Hackmann (*Rec. Trav. chim.*, 1932, **51**, 1157), which is formed from nicotyrine under similar conditions, is as Späth, Wibaut, and Kesztler claim (*Ber.*, 1938, **71**, 100), the Δ^3-derivative. Instances of 1 : 2(or 3 : 4)-addition in the reduction of pyrroles have been reported (Sonn, *Ber.*, 1935, **68**, 148; 1939, **72**, 2150), but they refer to compounds having substituents on the 3- or the 4-position of the pyrrole ring. Haines and Eisner (*J. Amer. Chem. Soc.*, 1950, **72**, 1719) have recently proved that the dihydronicotyrine is not, as Späth, Wibaut, and Kesztler supposed, identical with *N*-methylmyosmine, the Δ^2-pyrroline, and taking into account the acid stability of the dihydronicotyrine have decided that it is, in fact, the Δ^3-pyrroline, in agreement with our view.

Experimental.

3-*Benzylamino*-1 : 1-*diethoxypropane* (*Ethyl* 3-*Benzylaminopropionacetal*) (I).—The reaction between 3-chloro-1 : 1-diethoxypropane (*Org. Synth.*, Vol. XI, p. 26) (19 g., 1 mol.) and benzylamine (25 g., *ca.* 2 mols.) was slow at 100° and the mixture was therefore heated at 120—130° for 4 hours. When cold, the brown semi-solid mass was treated with 10% aqueous sodium hydroxide (60 c.c.), and the resulting oil extracted with ether and distilled. The fraction of b. p. 110—130°/3 mm. (14 g.) gave on redistillation ethyl 3-benzylamino-1 : 1-diethoxypropane as a colourless liquid, b. p. 140—144°/4 mm., which readily formed a *picrolonate*, crystallising from alcohol as stout yellow prisms, m. p. 178°, identical with that obtained from a specimen of the acetal prepared as by Wohl (*loc. cit.*) through reduction of 3-benzylideneamino-1 : 1-diethoxypropane (Found : C, 57·9; H, 6·2; N, 14·4. $C_{14}H_{23}O_2N,C_{10}H_8O_8N_4$ requires C, 57·5; H, 6·2; N, 14·0%).

When the acetal was added to an equivalent of 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid, precipitation of a solid quickly occurred. Crystallised from acetic acid, this *dinitrophenylhydrazone hydrochloride* formed glistening plates, m. p. 185° (decomp.) (Found : C, 50·5; H, 4·7. $C_{16}H_{17}O_4N_5,HCl$ requires C, 50·5; H, 4·7%). The corresponding *sulphate* was thrown down by the addition of water to a warm solution of the reagents in alcohol containing a few drops of sulphuric acid, and crystallised from acetic acid in small rectangular plates, m. p. 171° (Found : C, 43·4; H, 4·3; S, 6·8. $C_{16}H_{17}O_4N_5,H_2SO_4$ requires C, 43·5; H, 4·3; S, 7·2%).

2 : 4 : 6-*Tri*-(2-*benzylaminoethyl*)*trioxan* (III; R = $PhCH_2{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}$).—The above benzylaminoacetal (14 g.) was slowly dropped into concentrated hydrochloric acid (60 c.c.), stirred, and kept at 0°. The colourless solution was left at room temperature for 4 hours and then evaporated to dryness at 50° under reduced pressure. The residue was powdered under alcohol, thus giving a white solid (7 g., 62%) which was collected and dissolved in boiling alcohol with the addition of a small quantity of water. The 2 : 4 : 6-*tri*-(2-*benzylaminoethyl*)*trioxan hydrochloride* separated on cooling as a voluminous mass of colourless fine needles, m. p. 244° (decomp.) (Found, after drying at 157°/15 mm. for 2 hours : C, 60·4; H, 7·0; N, 6·8; Cl, 17·4. $C_{10}H_{13}ON,HCl$ requires C, 60·2; H, 7·0; N, 7·0; Cl, 17·8%). The salt does not reduce ammoniacal silver nitrate or hot Fehling's solution and forms benzylaminopropaldehyde 2 : 4-dinitrophenylhydrazone hydrochloride only slowly when heated or after a very prolonged time at room temperature. The action of boiling hydrochloric acid (50 c.c. of 10%) on the trioxan hydrochloride (5 g.) for 6 hours was to produce benzylamine, isolated as the hydrochloride, m. p. 256°, by evaporating the solution to dryness and stirring the residue with chloroform; the insoluble residue was then crystallised from alcohol–ethyl acetate. The well-washed pasty precipitate obtained from an acid solution of the trioxan hydrochloride and sodium nitrite gave Liebermann's nitroso-reaction.

The free trioxan *base* was obtained by shaking a cold aqueous solution of the hydrochloride with ether and magnesium oxide for 2 hours. The ether was evaporated under reduced pressure, a white solid appearing, but at room temperature the residue was a very pale straw-coloured oil which decomposed when heated at 0·05 mm. [Found : *M* (cryoscopically in 3% solution in benzene), after 1 day, 388; 2 days, 400; 4 days, 409; 5 days, 434; 8 days, 469; 14 days, 508; 60 days, 509. $(C_{10}H_{13}ON)_3$ requires *M*, 326; $(C_{10}H_{13}ON)_3$ requires *M*, 489].

A mixture of the base and aqueous oxalic acid gave a microcrystalline hydrated *hydrogen oxalate*, m. p. 234° (decomp.), which was recrystallised from water (Found, after drying at 100° under reduced pressure : C, 54·8, 54·9; H, 5·9, 6·4. $C_{10}H_{13}ON,C_2H_2O_4,\frac{1}{2}H_2O$ requires C, 55·0; H, 6·1%). The sparingly soluble *picrolonate*, m. p. 226° (decomp.), was prepared from the hydrochloride and potassium picrolonate in aqueous alcohol as a yellow powder, and could be recrystallised from nitrobenzene or *cyclo*hexanone (Found : C, 56·0; H, 4·8; N, 16·3. $C_{10}H_{13}ON,C_{10}H_8O_8N_4$ requires C, 56·1; H, 4·9; N, 16·4%). An alcoholic solution of the base mixed with the calculated quantity of dilute sulphuric acid and evaporated under reduced pressure gave the hydrated *hydrogen sulphate*, crystallising from alcohol in short, fine needles, m. p. 141° (Found, after drying at 100° under reduced pressure : C, 44·4; H, 6·1; S, 11·8. $C_{10}H_{13}ON,H_2SO_4,\frac{1}{2}H_2O$ requires C, 44·4; H, 5·9; S, 11·8%).

1 : 1-*Diacetoxy*-3-*N*-*benzylacetamidopropane*.—The trioxan hydrochloride (2 g.) was heated at 140°

with acetic anhydride (10 c.c.) until hydrogen chloride ceased to be evolved. The remaining anhydride was then evaporated under reduced pressure and the thin syrupy residue distilled. 1 : 1-*Diacetoxy*-3-N-*benzylacetamidopropane* was thus obtained as a colourless liquid, b. p. 170°/0·1 mm. (Found : C, 62·5; H, 6·9; N, 4·4; MeCO, 43·6. $C_{16}H_{21}O_4N$ requires C, 62·5; H, 6·8; N, 4·6; 3MeCO, 42·0%). When this was treated with a cold 2N-hydrochloric acid solution of 2 : 4-dinitrophenylhydrazine, 3-N-*benzylacetamidopropaldehyde dinitrophenylhydrazone* gradually formed, which crystallised from alcohol as a yellow powder, m. p. 133° (Found : C, 56·1; H, 5·0; N, 17·8. $C_{18}H_{19}O_6N_5$ requires C, 56·1; H, 4·9; N, 18·2%).

3-N-*Benzylacetamidoprop*-1-*enyl Ethyl Ether* (V).—3-Benzylamino-1 : 1-diethoxypropane (4·2 g.) was heated with acetic anhydride (20 c.c.) at 140—150° for 1 hour and the solution then distilled. The fraction of b. p. *ca.* 140°/0·4 mm. (3·9 g., 80%) was a colourless liquid which gave 3-*N*-benzylacetamidopropaldehyde 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 133°, and consisted of 3-N-*benzylacetamidoprop*-1-*enyl ethyl ether* (Found : C, 72·2; H, 8·2; N, 5·5; EtO, 18·3. $C_{14}H_{19}O_2N$ requires C, 72·1; H, 8·2; N, 6·0; EtO, 19·3%).

3-N-*Benzyl*-N-*cyanomethylamino*-1 : 1-*diethoxypropane*.—The acetal (I) (2·1 g.) was mixed with a saturated aqueous solution of sodium hydroxymethylenesulphonate (1·2 g.) and sufficient alcohol added to give a clear liquid. A solution of potassium cyanide (0·74 g.) in water (2—3 c.c.) was then introduced, which resulted in the appearance of an oil. After removal of the alcohol by aspiration of the hot mixture, this oil was extracted with ether and distilled. 3-N-*Benzyl*-N-*cyanomethylamino*-1 : 1-*diethoxypropane* (2 g.) was thereby obtained as a colourless liquid, b. p. 125°/0·05 mm. (Found : C, 69·4; H, 8·7; N, 9·8. $C_{15}H_{22}O_2N_2$ requires C, 69·5; H, 8·7; N, 10·1%). The 2 : 4-*dinitrophenylhydrazone sulphate* of the derived aldehyde separated on treatment of the acetal with a warm alcoholic sulphuric acid solution of the reagent, and was with some difficulty recrystallised from nitrobenzene–ethanol as an orange-brown powder, m. p. 165° (decomp.) (Found : C, 44·7; H, 3·8. $C_{18}H_{18}O_4N_6,H_2SO_4$ requires C, 44·8; H, 4·1%).

4-N-*Cyanomethylamino*-1 : 1-*diethoxypropane*.—4-Amino-1 : 1-diethoxybutane (2 g.) was dissolved in a saturated aqueous solution of sodium hydroxymethylenesulphonate (1·7 g.) and treated with a concentrated aqueous solution of potassium cyanide (0·8 g.). The oily layer which separated was removed by ether and distilled, giving the *cyanomethylamino-acetal* as a colourless liquid (2 g.), b. p. 90°/0·1 mm. (Found : C, 60·0; H, 10·0. $C_{10}H_{20}O_2N_2$ requires C, 60·0; H, 10·0%). The 2 : 4-*dinitrophenylhydrazone hydrochloride* of the derived aldehyde crystallised from nitromethane as a yellow microcrystalline powder, m. p. 160° (decomp.) (Found : C, 42·0; H, 4·6; N, 23·7; Cl, 9·6. $C_{12}H_{14}O_4N_6,HCl$ requires C, 42·1; H, 4·4; N, 24·5; Cl, 10·4%).

4-*Benzylideneamino*-1 : 1-*diethoxybutane*.—On the addition of benzaldehyde (5·3 g.) to 4-amino-1 : 1-diethoxybutane (8 g.) (Wohl, *Ber.*, 1906, **39**, 1952), heat was evolved and the mixture became turbid. The product was directly distilled, and the *benzylideneamino-acetal* (11·1 g.) obtained as a colourless and faintly odoriferous oil, b. p. 135°/0·04 mm. (Found : C, 72·1; H, 9·5; N, 5·6. $C_{15}H_{23}O_2N$ requires C, 72·3; H, 9·2; N, 5·6%).

4-*Benzylamino*-1 : 1-*diethoxybutane* (VI).—The above benzylidene compound (11 g.), dissolved in absolute ethanol (120 c.c.), was reduced by sodium (6 g.) added in ten portions to the solution boiling under reflux. Water (60 c.c.) was then introduced and the alcohol removed by drawing air through the solution heated on a steam-bath. Extraction of the cooled aqueous residue yielded the 3-*benzylamino-acetal* (9·8 g.) as a colourless mobile liquid, b. p. 133°/0·03 mm. (Found : C, 71·3; H, 9·9. $C_{15}H_{25}O_2N$ requires C, 71·7; H, 10·0%). The *picrolonate* crystallised from alcohol in yellow long rectangular plates, m. p. 146—147° (effervescence) (Found : C, 58·6; H, 6·6. $C_{25}H_{33}O_7N_5$ requires C, 58·3; H, 6·4%).

1-*Benzylpyrrolidine* (VII).—Distillation of the base liberated from a solution of the foregoing acetal which had been left in concentrated hydrochloric acid for several hours caused polymerisation. From the undistilled liquid a crystalline *picrolonate*, m. p. 140° (decomp.), sparingly soluble in ethanol, was obtained (Found, in a specimen dried at 70° : C, 58·6; H, 5·2; N, 15·7. $C_{11}H_{15}N,C_{10}H_8O_8N_4,\frac{1}{2}H_2O$ requires C, 58·4; H, 5·1; N, 16·1%).

The clear solution obtained by adding the 4-benzylamino-acetal (5 g.) to ice-cold concentrated hydrochloric acid (45 c.c.) was left for 4 hours at room temperature and then heated on a steam-bath with granulated tin (14 g.) for 1½ hours. The liquid was cooled, treated with excess of concentrated aqueous sodium hydroxide, and steam-distilled. Extraction of the distillate with ether isolated a colourless liquid (2·4 g.) which on fractionation gave 1-benzylpyrrolidine (1·9 g.), b. p. 245°, identified as the picrate, long hexagonal plates, m. p. 128°, first described by Schlinck (*Ber.*, 1899, **32**, 953) (Found : N, 14·4. Calc. for $C_{11}H_{15}N,C_6H_3N_3O_7$: N, 14·4%), and as the *picrolonate*, m. p. 137° (Found : C, 59·1; H, 5·7. $C_{11}H_{15}N,C_{10}H_8O_8N_4$ requires C, 59·3; H, 5·4%).

Ethyl N-α-*Cyanobenzylaminoacetate*.—Literature directions were followed for this preparation, the cyano-ester being isolated as hydrochloride. Stadnikoff (*loc. cit.*) found m. p. 82° (decomp.) and Scheibler and Baumgarten (*loc. cit.*) 83·5°; no analyses have been recorded. The unpurified product had m. p. 85—87° and, after it had been dried in a vacuum over calcium chloride, m. p. 95—97°. Crystallisation from ethanol–light petroleum gave the *cyano-ester hydrochloride* as colourless needles, m. p. 102° (decomp.) (Found : C, 56·9; H, 6·4; N, 11·0; Cl, 13·9. $C_{12}H_{14}O_2N_2,HCl$ requires C, 56·6; H, 6·0; N, 11·0; Cl, 13·5%).

N-α-*Carboxybenzylglycine* (VIII).—(i) The α-cyanobenzylaminoacetate hydrochloride (9 g.) was heated under reflux with hydrochloric acid (50 c.c. of 20%) for 90 minutes. The solution was evaporated to dryness on a steam-bath, and the solid residue dissolved, together with sodium acetate (5 g.), in water (50 c.c.). The amino-acid (1·8 g.) which separated during 2 days had m. p. varying with the preparation and with rate of heating, from *ca.* 202° to 218—220° (decomp.). Stadnikoff (*loc. cit.*) found m. p. 220° (decomp.), but samples prepared as above on recrystallisation from water showed m. p. 206—207° (decomp.) on rapid heating (Found : C, 57·6; H, 5·4; N, 6·7. $C_{10}H_{11}O_4N$ requires C, 57·4; H, 5·3; N, 6·7%).

(ii) The diethyl ester of this acid (2 g.) was heated under reflux with aqueous sodium hydroxide (20 c.c. of 2N.) for 90 minutes. The solution was then neutralised with 2N-hydrochloric acid, and on concentration and setting aside in the cold, the acid (VIII) crystallised, having m. p. after recrystallisation, 206—207° (decomp.) (Found: C, 57·5; H, 5·5; N, 6·6%).

Ethyl N-α-Carbethoxybenzylglycine.—To a solution of α-phenylglycine ethyl ester (65 g.) in ethanol (100 c.c.), chloroacetic acid (17 g.) in ethanol (50 c.c.) was slowly added, and after 3 hours' heating under reflux the solution was saturated with hydrogen chloride. After further heating for 3 hours the solvent was evaporated and the residue carefully shaken with benzene and aqueous sodium hydrogen carbonate. The dried benzene solution gave on distillation an oil (16 g.), b. p. 140—154°/1 mm., which was further purified by dilution with an equal volume of anhydrous ether, thereby next day causing the separation of a small quantity of solid. Redistillation of the filtered liquid gave ethyl *N*-α-carbethoxybenzylglycine (13·2 g.), b. p. 134°/0·5 mm., characterised by the following crystalline derivatives: (a) *Hydrochloride*, prepared in anhydrous ether, and crystallising from chloroform–light petroleum in needles, m. p. 114—115° (Found: C, 55·9; H, 6·6. $C_{14}H_{19}O_4N,HCl$ requires C, 55·7; H, 6·7%). (b) *Picrolonate*, crystallising from ethanol in clusters of prisms, m. p. 145—146° (Found: C, 54·8; H, 5·1. $C_{14}H_{19}O_4N,C_{10}H_8O_5N_4$ requires C, 54·45; H, 5·15%). (c) *Toluene-p-sulphonyl* derivative, obtained from a mixture of toluene-*p*-sulphonyl chloride (2·3 g.), ester (3·2 g.), and pyridine (6 c.c.), which after 2 days at room temperature was poured into water, washed in ethereal solution with acid, and crystallised from light petroleum containing a little benzene; it formed prisms, m. p. 64—65° (Found: C, 60·6; H, 6·2; N, 3·7. $C_{28}H_{33}O_6NS$ requires C, 60·1; H, 6·0; N, 3·35%).

2-Phenyl-Δ³-pyrroline (cf. Gitsels and Wibaut, *Rec. Trav. chim.*, 1940, **59**, 1102) (II).—A solution of 2-phenylpyrrole (4·8 g.) in ethanol (15 c.c.) containing zinc dust (15 g.) was stirred and heated under reflux for 2 hours during the gradual addition of hydrochloric acid (30 c.c. of 20%, followed by 20 c.c. of 30%). After refluxing for a further hour, the liquid was cooled, decanted from residual zinc, and made strongly alkaline with aqueous sodium hydroxide. The mixture was then steam-distilled and the distillate acidified with concentrated hydrochloric acid. When non-basic material had been removed by ether the solution was again basified, and further ether-extraction gave 2-phenyl-Δ³-pyrroline as a colourless oil (4 g.), b. p. 112—113°/11 mm., which was identified by the picrate, m. p. 139—140° (140—141°, Gitsels and Wibaut, *loc. cit.*) (Found: C, 51·3; H, 4·0. Calc. for $C_{10}H_{11}N,C_6H_3O_7N_3$: C, 51·35; H, 3·8). The *toluene-p-sulphonyl* derivative (0·5 g.), prepared by shaking the pyrroline (0·35 g.) and toluene-*p*-sulphonyl chloride (0·7 g.) in aqueous sodium hydroxide (5 c.c.; 2N.) containing acetone (1 c.c.), crystallised from aqueous alcohol in long needles, m. p. 124—125° (Found: C, 68·1; H, 5·9. $C_{17}H_{17}O_2NS$ requires C, 68·2; H, 5·7%).

Oxidation of 2-Phenyl-Δ³-pyrroline.—Ozonised oxygen was passed for 2 hours into a solution of 2-phenyl-Δ³-pyrroline (2 g.) in 2N-hydrochloric acid (20 c.c.) at 0°. Hydrogen peroxide (5 c.c.; 40-vol.) was then added to the clear pale yellow solution, and 2 hours later the excess was destroyed by warming in presence of platinum wire to 60°. The solution was concentrated to small bulk at 40° under low pressure and treated with sodium acetate (1 g.) but, since after the mixture had been kept at 0° only a little tarry material separated, the remaining water was removed, an operation which led to further decomposition, the dark residue smelling of benzaldehyde. The dried product was heated under reflux with alcoholic hydrogen chloride, and the resulting ester (1 g.) isolated in the usual manner. It gave with picrolonic acid (1 g.) a product (1·6 g.), m. p. 142—146°, which after recrystallisation from acetone–ether and finally ethanol had m. p. 145—146° alone or mixed with the picrolonate of ethyl *N*-α-carbethoxybenzylglycine. The ester which was recovered from the dried chloroform layer after shaking a chloroform solution of the crystallised picrolonate with aqueous lithium hydroxide, gave the hydrochloride, m. p. and mixed m. p. 114—115°, and was hydrolysed to give *N*-α-carboxybenzylglycine, m. p. 206—207 (decomp.).

DYSON PERRINS LABORATORY, OXFORD UNIVERSITY.
THE UNIVERSITY, NOTTINGHAM.

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56. *Syntheses from Phthalimido-acids. Part II. Further Reactions of Phthalylglutamic Anhydride.*

By F. E. KING, B. S. JACKSON, and D. A. A. KIDD.

The action of methanol and of benzyl alcohol on phthalyl-DL-glutamic anhydride gives monoesters, shown to be γ-derivatives by hydrolysis of the phthalyl group with hydrazine to give compounds of recognisable constitution. This parallels the formation of γ-amides from phthalyl-DL- and -L-glutamic anhydrides with ammonia, etc., which has resulted in an improved synthesis of glutamine (King and Kidd, *Nature*, 1948, **162**, 776; *J.*, 1949, 3315).

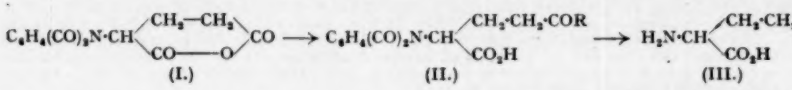
Hydrazine reacts preferentially with the anhydride ring of phthalylglutamic anhydride, as is evident in the production of a hydrazide which is converted *via* the azide into the known phthalyl-γ-DL-glutamylanilide.

IN a recent communication (King and Kidd, *J.*, 1949, 3315) which is to be regarded as Part I of this series, an account was given of the preparation and some reactions of phthalyl-DL- and

-L-glutamic anhydrides already cursorily reported (*Nature*, 1948, **162**, 776). Remarkable among the properties of these anhydrides is their conversion, by ammonia and by certain amines and amino-acids, into γ-amides, thus providing—in contrast to the usual method employing carbobenzyloxyglutamic anhydride (Bergmann and Zervas, *Ber.*, 1933, **66**, 1288)—a direct synthesis of glutamine.

The reactions of phthalyl-DL-glutamic anhydride have since been further investigated, and the results indicate that cleavage of the anhydride ring to form γ-derivatives is a general property. For example, the crystalline product obtained by heating a solution of the DL-anhydride in methanol is γ-methyl hydrogen phthalyl-DL-glutamate (II; R = OMe), and it can be hydrolysed with aqueous hydrazine under the mild conditions described in Part I to γ-methyl hydrogen DL-glutamate (III; R = OMe). The constitution of this acid ester, and hence of its precursor, rests on its identity with that prepared by partial esterification of DL-glutamic acid following the conditions first determined by Abderhalden and Nienberg (*Z. physiol. Chem.*, 1933, **219**, 155) for the ethyl ester of the L-isomer. Though wrongly oriented at the time, the product thus prepared is the γ-ester (see Bergmann and Zervas, *ibid.*, 1933, **221**, 51; Nienberg, *Ber.*, 1935, **68**, 2232), a fact which is further demonstrated by the recent application of the method to the synthesis of what is undoubtedly γ-ethyl hydrogen DL-glutamate (King and Spensley, *J.*, 1950, 3159).

Similarly, the anhydride gave a high yield of γ-benzyl hydrogen phthalyl-DL-glutamate (II; R = O·CH_2Ph) when heated at 100° with excess of benzyl alcohol and, by adopting the well-known procedure of Bergmann and Zervas (*loc. cit.*) for the synthesis of L-glutamine, this derivative was made the starting point for a series of reactions leading to the hitherto



unknown DL-*iso*glutamine. The ester-acid chloride prepared with phosphorus pentachloride was treated with ethereal ammonia, so forming phthalyl-DL-*iso*glutamine benzyl ester. Hydrogenolysis afforded phthalyl-DL-*iso*glutamine, and removal of the phthalyl group with hydrazine left DL-*iso*glutamine. With the exception of the acid chloride, which was not purified, all stages were isolated as crystalline compounds in very satisfactory yields. The properties of the intermediate phthalylglutamide show it to be distinct from the authentic phthalyl-DL-glutamine (King and Kidd, *loc. cit.*), thus confirming the supposition, based on analogy with the methanol reaction, that treatment of phthalyl-DL-glutamic anhydride with benzyl alcohol yields the γ-glutamate.

The effect of hydrazine on the phthalylglutamic anhydride was also examined to ascertain whether a hydrazide might be obtained without severing the protecting group. The product obtained by treating a dioxan solution of the anhydride with one molecular portion of hydrazine hydrate was conveniently recovered by shaking the product with benzaldehyde, whereby phthalyl-DL-glutamyl-γ-benzylidenehydrazide (II; R = NH·N:CHPh) (85%) was obtained. This derivative was also formed when phthalyl-DL-glutamic anhydride in ethyl acetate–chloroform was shaken with aqueous sodium hydrogen carbonate and benzylidenehydrazine. The constitution of the hydrazide was determined by dissolving it in hydrochloric acid and adding sodium nitrite. The ether-soluble portion (31%) of the product displayed the normal reactions of an azide, and when mixed with aniline gave phthalyl-DL-glutamyl-γ-anilide (II; R = NHPh) identical with that prepared and oriented as described in Part I.

When the phthalylglutamic anhydride was treated with excess of hydrazine, the formation of phthalhydrazide showed, as was to be expected, that hydrolysis of this phthalyl group had also occurred.

Experimental.

γ-Methyl Hydrogen Phthalyl-DL-glutamate (II; R = OMe).—Phthalyl-DL-glutamic anhydride (I) (5 g.) was refluxed with methyl alcohol (65 c.c.), heating being continued for ½ hour after the solid had dissolved. Removal of excess of methanol under reduced pressure left a syrup which was extracted with aqueous sodium hydrogen carbonate. The filtered solution was acidified with hydrochloric acid to Congo-red and kept overnight at 0°. Colourless needles of the *ester hydrate* separated, m. p. 60—62° (Found: loss in a vacuum at 110°, 8·1. $C_{14}H_{13}O_6N,1\frac{1}{2}H_2O$ requires loss, 8·4%), which when dried at 100° under reduced pressure gave γ-methyl hydrogen phthalyl-DL-glutamate as prisms (from benzene–light petroleum), m. p. 114° (Found: C, 57·4; H, 5·0; N, 4·8. Calc. for $C_{14}H_{13}O_6N$: C, 57·7; H, 4·5; N, 4·8%). Sheehan and Bolhofer (*J. Amer. Chem. Soc.*, 1950, **72**, 2471) give m. p. 119·5—120·5° (corr.).

γ-Methyl Hydrogen DL-*Glutamate* (III; R = OMe).—(i) DL-Glutamic acid hydrochloride (8·45 g.) was shaken with methanol (70 c.c.) containing hydrogen chloride (6 g.), and after 20 minutes the solution was filtered and concentrated at 20° under diminished pressure. Addition of dry ether gave a syrup which was dissolved in methanol (50 c.c.) containing aqueous ammonia (2·5 c.c.; *d* 0·88). After this had been kept at 0°, a white precipitate (2 g., 27%) appeared, which when crystallised from aqueous methanol gave *γ-methyl hydrogen* DL-*glutamate*, m. p. 183° (decomp.) (Found: C, 44·9; H, 7·0; N, 8·5. $C_6H_{11}O_4N$ requires C, 44·8; H, 6·9; N, 8·7%). The pure ester gave a violet colour with ninhydrin reagent.

(ii) γ-Methyl hydrogen phthalyl-DL-glutamate (2 g.), dissolved in water (25 c.c.) containing sodium carbonate (0·2 g.), was treated with hydrazine hydrate (0·7 g.; 50%), and the mixture left at room temperature for 48 hours. The precipitate of phthalhydrazide which appeared on acidification with hydrochloric acid was removed and the filtrate evaporated to dryness at low pressure. Trituration of the residue with cold methyl alcohol and concentration of the alcoholic extract gave the hydrochloride of γ-methyl hydrogen DL-glutamate which on treatment with anhydrous ether formed a flocculent highly deliquescent solid (0·8 g.). Dissolved in methanol and treated with aqueous ammonia (0·24 g.; *d* 0·88), it gave, after 12 hours at 0°, the monoester (0·6 g., 54%), m. p. and mixed m. p., after crystallisation from aqueous ethanol, 183°.

*γ-Benzyl Hydrogen Phthalyl-*DL-*glutamate* (II; R = O·CH_2Ph).—Phthalyl-DL-glutamic anhydride (8 g.) was heated with benzyl alcohol (12 g.) at 100° until a clear solution was obtained. Ether was then added and the ethereal solution extracted with aqueous sodium hydrogen carbonate. The combined extracts were washed with ether and acidified with hydrochloric acid, the precipitated oil being taken up in ether. Drying and evaporation of the ethereal solution left a gum (10·2 g., 90%) which solidified in contact with benzene, and crystallisation from benzene–light petroleum gave *γ-benzyl hydrogen phthalyl-*DL-*glutamate* as colourless soft needles, m. p. 85—86° (Found: C, 65·7; H, 4·75; N, 4·1. $C_{20}H_{17}O_6N$ requires C, 65·5; H, 4·6; N, 3·8%).

*Phthalyl-*DL-iso*glutamine Benzyl Ester.*—A solution of the γ-benzyl hydrogen phthalylglutamate (6·7 g.) in dry ether (50 c.c.) was shaken with phosphorus pentachloride (3·92 g.), with occasional cooling in ice-water, until reaction was complete. The pale yellow syrup left on removal of the ether was well washed with light petroleum and then redissolved in ether. Ethereal ammonia was added until precipitation ceased and, after collection, the solid was triturated with dilute aqueous sodium hydrogen carbonate. The residue of *phthalyl-*DL-iso*glutamine benzyl ester* (6·1 g., 91%) crystallised from water in minute felted needles, m. p. 126—128° (Found: C, 66·0; H, 4·9; N, 7·5. $C_{20}H_{18}O_5N_2$ requires C, 65·5; H, 4·9; N, 7·6%).

*Phthalyl-*DL-iso*glutamine.*—The foregoing benzyl ester (4 g.) in aqueous ethanol (100 c.c.) containing acetic acid (0·5 c.c.) was hydrogenated over palladium–charcoal at 1—2 atmospheres pressure and 40—60°. The residue obtained on evaporating the filtered solution to dryness was shaken with aqueous sodium hydrogen carbonate, and the soluble portion precipitated with hydrochloric acid. The deposited *phthalyl-*DL-iso*glutamine* (2·6 g., 87%) crystallised from aqueous alcohol in fine needles, m. p. 170—172° with shrinkage at 100—120° (Found: loss on drying in a vacuum at 110°, 5·9. $C_{13}H_{12}O_5N_2.H_2O$ requires loss, 6·1%. Found, in dried material: C, 57·1; H, 4·3; N, 10·0. $C_{13}H_{12}O_5N_2$ requires C, 56·5; H, 4·4; N, 10·1%).

DL-iso*Glutamine.*—Phthalyl-DL-*iso*glutamine (1·3 g.) was dissolved in aqueous sodium carbonate (1 equiv. of 0·5N.) to which hydrazine hydrate (0·45 g.; 50%) was then added. After 48 hours at 0°, the solution was acidified with excess of 3N-hydriodic acid, and the precipitate of phthalhydrazide collected. The filtrate was exactly neutralised with 0·5N-sodium carbonate, and the solution evaporated to small bulk at low pressure. Addition of acetone precipitated DL-iso*glutamine* (0·35 g., 55%) which could be obtained in clusters of needles (Found: N, 19·3. $C_5H_{10}O_3N_2$ requires N, 19·2%) when rapidly crystallised from aqueous acetone but was contaminated by ammonium glutamate when crystallisation was slow. Alternatively, phthalyl-DL-*iso*glutamine (1 g.) was dissolved in aqueous hydrazine (1·11 g. of 19·6%, 2 mols.) and after 48 hours at 0° the phthalylhydrazide was precipitated with acetic acid, the *iso*glutamine being obtained from the filtrate by the addition of acetone. DL-*iso*Glutamine does not melt but slowly chars above 180°. It gives a magenta colour with ninhydrin reagent.

*Phthalyl-*DL-*glutamyl-γ-benzylidenehydrazide* (II; R = NH·N:CHPh).—(i) A solution of phthalyl-DL-glutamic anhydride (2 g.) in dioxan (25 c.c.) was treated with hydrazine hydrate (1·8 g. of 50%, 2 mols.) in dioxan (25 c.c.), added in portions with water-cooling. Anhydrous ether was then introduced and, after being kept at 0°, the deliquescent precipitate was separated by decantation and dissolved in water (25 c.c.). After the addition of sodium hydrogen carbonate (0·65 g.) and benzaldehyde (2·6 g.), the mixture was shaken for an hour and the precipitate of benzaldazine removed. Acidification with hydrochloric acid gave *phthalyl-*DL-*glutamyl-γ-benzylidenehydrazide* as a pale straw-coloured mass (2·5 g., 85%) which after being washed with ether and crystallised from aqueous alcohol or ethyl acetate–light petroleum formed minute prisms, m. p. 136—138° (Found: C, 63·4; H, 4·8; N, 11·0. $C_{20}H_{17}O_4N_3$ requires C, 63·4; H, 4·5; N, 11·1%).

(ii) A mixture of the glutamic anhydride (2 g.) in chloroform–ethyl acetate (50 c.c. of each) and of sodium hydrogen carbonate (1 g.) in water (25 c.c.) was vigorously shaken with benzylidenehydrazine (1 g.), added in portions. On removal of the aqueous layer and acidification with hydrochloric acid, the phthalylglutamylbenzylidenehydrazide separated and after crystallisation had m. p. and mixed m. p., 136—137°.

When a suspension of the anhydride in water was treated with excess of hydrazine, dissolution quickly occurred, and acidification with hydrochloric acid followed by the addition of sodium acetate caused the precipitation of phthalhydrazide. No attempt was made to isolate the amino-acid moiety.

*Phthalyl-*DL-*glutamyl-γ-anilide* (II; R = NHPh).—The phthalylglutamic anhydride (2 g.) was treated with hydrazine hydrate as described above, and the deliquescent solid precipitated by ether

was dissolved without removal of the organic layer in 2N-hydrochloric acid (100 c.c.). Aqueous sodium nitrite (10%) was added, using starch–iodide indicator, and the ethereal layer separated, washed, and dried (Na_2SO_4). Evaporation at low temperature left minute white prisms (0·7 g., 31%), decomposing at *ca.* 60° with effervescence. When aniline (0·8 g.) was added to the ethereal solution, which was then set aside for 1—2 days, a pale buff powder was slowly deposited. This could be crystallised from water containing a little hydrochloric acid (charcoal) to yield colourless prisms, m. p. 106—108°, alone or mixed with phthalyl-DL-glutamyl-γ-anilide prepared from phthalyl-DL-glutamic anhydride and aniline by King and Kidd (*loc. cit.*, p. 3318).

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57. *The Synthesis of Pantothenic Acid-2′ and -4′ Phosphates as Possible Degradation Products of Coenzyme A.*

By J. BADDILEY and E. M. THAIN.

The two monophosphates of pantothenic acid have been synthesised by unambiguous routes for comparison with certain degradation products of coenzyme A, the factor involved in biological acetylation processes. Rates of acid hydrolysis of the phosphate bonds have been measured for both compounds.

Neither of these phosphates stimulated the growth of *Acetobacter suboxydans*. The structure of coenzyme A is discussed in the light of these results.

THE importance of acetylation in living systems has become increasingly evident during the last few years. Acetylation of choline has long been recognised as a fundamental reaction in the chemistry of nerve action, and acetoacetic acid is a well-known metabolic product of acetic acid, but only lately has it been realised that acetylation is of great significance in other cellular transformations. The discovery by Lipmann (*Enzymologia*, 1937, **4**, 65; *Cold Spring Harbor Symposia*, 1939, **7**, 248; *Advances in Enzymology*, 1946, **6**, 231) of acetyl phosphate in *Lactobacillus delbrückii* and the demonstration that this was an active acetylating agent in enzymic reactions stimulated much subsequent work. "Energy-rich" acetylating agents, possibly chemically related to acetyl phosphate, are believed to participate in the complex cyclic processes involved in the metabolism of carbohydrates (Krebs, *Advances in Enzymology*, 1943, **3**, 191; Martius and Lynen, *ibid.*, 1950, **10**, 167). The presence of a co-factor of general occurrence has been shown to be necessary for the acetylation of aromatic amines by liver preparations (Lipmann, *Fed. Proc.*, 1945, **4**, 97; *J. Biol. Chem.*, 1945, **160**, 173) and of choline in brain (Lipmann and Kaplan, *J. Biol. Chem.*, 1946, **162**, 743). This factor, which is also active in other biological acetylation systems (Stern and Ochoa, *ibid.*, 1949, **179**, 491), has been called "coenzyme A," and hydrolysis of its highly active concentrates yields pantothenic acid (Lipmann, Kaplan, Novelli, Tuttle, and Guirard, *ibid.*, 1947, **167**, 869). The importance of this finding was increased when it was shown that most cellular pantothenic acid is present as either coenzyme A or closely related factors in both animals and plants (Kaplan and Lipmann, *ibid.*, 1948, **174**, 37; Novelli, Kaplan, and Lipmann, *ibid.*, 1949, **177**, 97; King, Fels, and Cheldelin, *J. Amer. Chem. Soc.*, 1949, **71**, 131). Intestinal phosphatase and pigeon-liver extracts inactivate coenzyme A, liberating pantothenic and phosphoric acids (Novelli, Kaplan, and Lipmann, *loc. cit.*), whence it seems probable that the coenzyme is a phosphorylated derivative of pantothenic acid. Coenzyme A itself stimulates the growth of *Lactobacillus arabinosus*, but the liver extract degradation product does not. However, this fragment is active in stimulating the growth of *Acetobacter suboxydans*, a property which is destroyed by treatment with intestinal phosphatase (Novelli, Flynn, and Lipmann, *J. Biol. Chem.*, 1949, **177**, 493). It would seem, therefore, that *A. suboxydans* can utilise a fragment of coenzyme A which exhibits the properties of a phosphoric ester of pantothenic acid. Recent enzymic experiments suggest that the coenzyme itself is a dinucleotide (Novelli, Kaplan, and Lipmann, *Fed. Proc.*, 1950, **9**, 209). The present work describes the synthesis of two isomeric phosphoric esters of pantothenic acid (I; R = R″ = H, R′ = PO_3H_2) and (I; R = R′ = H, R″ = PO_3H_2), with the expectation that one of them might be identical with the liver-extract degradation product of coenzyme A. Results of biological tests on the two esters are discussed below.

The method we envisaged for the synthesis of (±)-*N*-(4′-hydroxy-3′ : 3′-dimethyl-2′-phosphonoxybutyro)-β-alanine,* for convenience called (±)-pantothenic acid-2′ phosphate * (I; R = R″ = H, R′ = PO_3H_2), involved the direct phosphorylation of pantolactone (II) and reaction of the resulting phosphate with a suitable derivative of β-alanine, as in the synthesis of pantothenic acid from pantolactone (Williams, Mitchell, Weinstock, and Snell, *J. Amer. Chem. Soc.*, 1940, **62**, 1784). Phosphorylation of pantolactone with phosphoryl chloride did not give any recognisable product, and experiments with dibenzyl chlorophosphonate were equally unsuccessful since the unreactive secondary hydroxyl group in pantolactone is not phosphorylated at the low temperatures required. However, with diphenyl chlorophosphonate in anhydrous pyridine at 0° pantolactone was converted smoothly and in good yield into the crystalline diphenyl phosphate ester (III), which could be purified by distillation at low pressure. When this ester was heated with the sodium salt of β-alanine under conditions similar to those employed in the preparation of pantothenic acid from pantolactone (Williams, *et al.*, *loc. cit.*) a complex reaction occurred. On addition of water, phenol was liberated and from the aqueous solution only nitrogen-free phosphorylated products could be isolated by precipitation with lead acetate. The reaction was repeated under a wide variety of conditions, employing both sodium and lithium salts of β-alanine, but without success. In an effort to clarify the nature of this unexpected reaction, (III) was heated with an excess of *cyclo*hexylamine. A water-soluble, crystalline product, $C_{18}H_{35}O_5N_2P$, was isolated, which can be regarded as derived from one molecule of (III) and two molecules of base with elimination of both phenyl groups and an oxygen atom. One molecule of base is probably involved in amide linkage with the carbonyl group of (III) while the other may have displaced a phenoxy-group to give an aminophosphonate. With ammonia in alcohol at 30° the lactone (III) yielded small amounts of a substance, $C_{12}H_{19}O_5N_2P$, which is probably an aminophosphonate containing a residual phenoxy-group. Further work on the structure of these substances is in progress.

(I.) $R''O{\cdot}CH_2{\cdot}CMe_2{\cdot}\underset{\displaystyle OR'}{CH}{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2R$

$CH_2{-}CMe_2{-}\underset{\displaystyle O}{CH}{\cdot}OR$ (II; R = H.) (III; R = PO_2Ph_2.)
$O{-}\!\!-\!\!-\!\!-\!\!-{-}CO$

$HO{\cdot}CH_2{\cdot}CMe_2{\cdot}\underset{\displaystyle O{\cdot}PO_3H_2}{CH}{\cdot}CO{\cdot}NH{\cdot}C_6H_{11}$ (VI.)

(IV; R = PO_3H_2.) (V; R = CH_2Ph.)

It seemed likely that the difficulties encountered in the reaction of β-alanine derivatives with (III) arose through the presence of the two phenyl groups. Consequently, these were removed by hydrogenolysis and the resulting pantolactone-2′ phosphate (IV) was characterised by its behaviour with alkali. It consumed two equivalents of sodium hydroxide in the cold and a further equivalent on warming; thereafter, pantolactone-2′ phosphate could be recovered as its crystalline *cyclo*hexylamine salt. It followed that (IV) was both a monophosphate and a lactone. In order to demonstrate that it would behave normally with amines a sample was heated with *cyclo*hexylamine, and the product, isolated *via* the lead salt, was converted into its monostrychnine salt. Analysis of this agreed with that expected for the strychnine salt of (VI).

A more satisfactory method of forming the amide link between (IV) and β-alanine was then sought utilising the benzyl ester of β-alanine (Kuhn and Wieland, *Ber.*, 1940, **73**, 971). A syrup was obtained which presumably consisted of the benzyl ester (I; R = CH_2Ph, R′ = PO_3H_2, R″ = H) of pantothenic acid 2′-phosphate in the form of its salt with β-alanine benzyl ester, together with the decomposition products of β-alanine benzyl ester. A barium salt obtained from the crude benzyl ester appeared from its barium content to have lost a part of its benzyl group by hydrolysis during isolation. Removal of the benzyl group was then completed by hydrogenolysis, and (±)-pantothenic acid 2′-phosphate (I; R = R″ = H, R′ = PO_3H_2) was isolated in good yield as its barium salt.

The synthesis of the isomeric 4′-phosphate (I; R = R′ = H, R″ = PO_3H_2) necessitated protection of the secondary hydroxyl group before phosphorylation. Pantolactone readily formed a sodio-derivative when treated with powdered sodium or sodium ethoxide (cf. Fleck and Schinz, *Helv. Chim. Acta*, 1950, **33**, 140); with benzyl chloride in hot xylene this gave the crystalline benzyl ether (V) in good yield. The presence of a lactone ring in this substance was demonstrated by its behaviour with alkali. Reaction of (V) with the sodium salt of β-alanine gave the benzyl ether (I; R = R″ = H, R′ = CH_2Ph) as a syrup, the structure of which followed from hydrogenolysis to pantothenic acid. Diphenyl chlorophosphonate converted

* Geneva numbering (CO_2H = 1) is used throughout this paper for the butyric acid derivatives.

(I; R = R″ = H, R′ = CH_2Ph) in anhydrous pyridine into a syrup (I; R = H, R′ = CH_2Ph, R″ = PO_3Ph_2). Hydrogenolysis of benzyl and phenyl groups from this proceeded smoothly and the resulting (±)-pantothenic acid 4′-phosphate was purified through either its silver or its lead salt and isolated as its barium salt. Alternatively the benzyl ether (V) was treated with β-alanine benzyl ester giving (I; R = R′ = CH_2Ph, R″ = H) which had the expected structure since it could be hydrogenated to pantothenic acid; this ester was phosphorylated with diphenyl chlorophosphonate to (I; R = R′ = CH_2Ph, R″ = PO_3Ph_2), and both benzyl and phenyl groups were removed by hydrogenolysis; the resulting (±)-pantothenic acid 4′-phosphate was isolated and purified as before

During this work it was observed that both diphenyl and dibenzyl phosphates form readily crystalline *S*-benzylthiuronium salts which have sharp melting points and are quite useful alternatives to the *cyclo*hexylamine salts for identification of these esters.

The two phosphates of pantothenic acid resembled each other closely in general physical properties. However, the phosphate group of the 4′-phosphate is more labile to acid than is that of the 2′-phosphate. In 2N-hydrochloric acid at 100° the 4′-phosphate was 50% and the 2′-phosphate was only 11% hydrolysed in 150 minutes. The 2′-phosphate showed first-order kinetics, k being $1{\cdot}1 \times 10^{-5}$ sec.$^{-1}$; pantolactone 2′-phosphate was hydrolysed at the same rate and is thus probably an intermediate in the hydrolysis of pantothenic acid 2′-phosphate. The 4′-phosphate gave a first-order velocity constant of $6{\cdot}9 \times 10^{-6}$ sec.$^{-1}$ up to approximately 60% hydrolysis, but subsequently the rate fell to approximately that of the 2′-phosphate. The 2′- and the 4′-phosphate showed considerable stability toward alkali, no measurable hydrolysis occurring in 2 hours at 100° in 0·5N-potassium hydroxide.

The two pantothenic acid phosphates have been examined as stimulants for the growth of *A. suboxydans* by Dr. F. Lipmann, to whom we express our thanks. He reports that neither isomer showed growth stimulation or replaced free pantothenic acid. No inhibition was observed in either case and after treatment with alkaline phosphatase the expected growth response was observed from both substances corresponding to the liberation of free pantothenic acid. It would seem then that neither phosphate represents an active degradation product of coenzyme A and we are inclined to conclude that either the active substance is more complex and contains further substituents on the pantothenic acid residue besides phosphate or that phosphate is linked to pantothenic acid through some other component. However, through the kindness of Dr. F. Bergel, the two substances have been examined by Roche Products Ltd., for pharmacological effects on gut: in preliminary experiments both phosphates caused a slow but quite marked contraction of isolated rabbit and guinea-pig ileum. Under the conditions of the experiment neither pantothenic acid nor phosphate showed the effect. It is not possible at this stage to discuss the mechanism of this action. Further work on the relation between these phosphates and coenzyme A is in progress.

Experimental.

(±)-3 : 3-*Dimethylbutyro-γ-lactone* 2-(*Diphenyl Phosphate*) (III).—Diphenyl chlorophosphonate (8·5 g.) was added slowly to a stirred solution of pantolactone (4 g.) in anhydrous pyridine (40 c.c.) at 0°. After the mixture had been kept for 1 hour at 0° and 12 hours at room temperature water (10 c.c.) was added and the resulting solution evaporated under reduced pressure below 45°. The residue was dissolved in chloroform (60 c.c.), washed with dilute sulphuric acid, sodium hydrogen carbonate solution, and water, and finally evaporated under reduced pressure. The syrupy residue crystallised slowly. The *phosphate* was purified either by recrystallisation from ether–light petroleum (b. p. 40—60°), as prisms, m. p. 70°, or by sublimation in a short-path still at 150°/10^{-4} mm. (yield 10 g., 90%) (Found: C, 60·0; H, 5·1; P, 8·3. $C_{18}H_{19}O_6P$ requires C, 59·7; H, 5·2; P, 8·6%).

Reaction with cyclo*Hexylamine.*—A mixture of *cyclo*hexylamine (1·1 g.) and (III) (1 g.) was heated on a steam-bath for 5½ hours. The resulting syrup was dissolved in ether and shaken with water (3 × 10 c.c.). Evaporation of the combined aqueous extracts under reduced pressure left a resin which was dissolved in a little alcohol, and ether was added to incipient opalescence. Fine needles separated. Recrystallised from alcohol–ether the *substance* had m. p. 253° (0·5 g.) (Found: C, 55·2; 55·3; H, 9·1, 9·0; N, 6·7. $C_{18}H_{35}O_5N_2P$ requires C, 55·3; H, 9·0; N, 7·1%).

Reaction with Ammonia.—A solution of (III) (1 g.) in 10% alcoholic ammonia (100 c.c.) was kept at 30° for 5 minutes, then at room temperature for 1 hour. A crystalline *substance* was filtered off and recrystallised from acetic acid; it had m. p. 220° (Found, in substance dried at 110°/10^{-4} mm.: C, 47·1; H, 6·4; N, 9·1; P, 9·8. $C_{12}H_{18}O_5N_2P$ requires C, 47·5; H, 6·3; N, 9·2; P, 10·2%).

(±)-3 : 3-*Dimethylbutyro-γ-lactone* 2-*Phosphate* (IV).—A solution of the diphenyl ester (III) (11 g.) in acetic acid (200 c.c.) was hydrogenated at atmospheric pressure and room temperature with a platinum oxide catalyst. After absorption of hydrogen had ceased (8 mols. absorbed at about 900 c.c. per hour) the catalyst was filtered off and solvent removed by distillation at reduced pressure. The residue crystal-

lised slowly as needles and traces of acetic acid were removed by rubbing them with ether. The *phosphate* had m. p. 130—140° (5·6 g., 90%) (Found : C, 35·0; H, 5·0; P, 14·9. $C_9H_{11}O_8P$ requires C, 34·5; H, 5·2; P, 14·8%). It readily formed a *cyclohexylamine* salt which, recrystallised from alcohol, had m. p. 202—203° (Found : C, 46·5; H, 7·6; N, 4·5. $C_9H_{11}O_8P,C_6H_{13}N$ requires C, 46·5; H, 7·7; N, 4·5%). On titration (phenolphthalein) at room temperature the phosphate (100 mg.) consumed 9·31 ml. of 0·1N-sodium hydroxide (theor., 9·52 ml.). A further 5 ml. were consumed slowly on warming. The resulting solution did not give a precipitate with barium acetate solution, indicating the absence of hydrolysis of the phosphate residue during titration. Hydrochloric acid (1·23 ml.; 1·124N.), equivalent to the alkali consumed, was added and the solution evaporated to dryness under reduced pressure. The residue was treated with *cyclo*hexylamine and the *cyclo*hexylamine salt of (IV) extracted with hot alcohol. Recrystallised from alcohol it had m. p. 190—193° and mixed with authentic material, m. p. 195—196°.

(±)-N-cyclo*Hexyl*-4-*hydroxy*-3 : 3-*dimethyl*-2-*phosphonoxybutyramide* (VI).—To a mixture of pantolactone 2-phosphate (0·6 g.) and *cyclo*hexylamine (4 c.c.) on a steam-bath, sufficient alcohol was added to effect dissolution at the b. p. Solvent was then distilled off slowly and the remaining oil heated at 100° for 2 hours. Excess of *cyclo*hexylamine was removed at 100°/10^{-4} mm. The residue was dissolved in water, and addition of lead acetate solution precipitated a lead salt. This was collected by centrifugation, washed well with water, and dried over sulphuric acid in a desiccator (0·9 g.). The lead salt was dissolved in aqueous alcohol, and lead removed by precipitation as the sulphide. The filtered solution was evaporated under reduced pressure, leaving a brittle resin. This did not crystallise but formed a *strychnine* salt, m. p. 160—170°, after recrystallisation from alcohol–ether (Found, in sample dried at 100° : C, 61·8; H, 7·1; N, 6·3. $C_{12}H_{24}O_8NP,C_{21}H_{22}O_2N_2$ requires C, 61·6; H, 7·1; N, 6·5%).

(±)-*Pantothenic Acid* 2′-*Phosphate* (I; R = R″ = H, R′ = PO_3H_2).—Pantolactone 2-phosphate (3·8 g.) was mixed with dry, freshly prepared β-alanine benzyl ester (12·8 g.) (prepared by the method of Kuhn and Wieland, *loc. cit.*) and the mixture heated at 100° for 6 hours with the exclusion of moisture and carbon dioxide. The reaction mixture was cooled to room temperature and dissolved in water (50 c.c.), and barium hydroxide solution (107 c.c. of 0·34N.) added. After evaporation of the mixture to small volume under reduced pressure, alcohol (150 c.c.) was added and the precipitated barium salt centrifuged, washed twice with alcohol, then once with ether, and dried in an oven at 100°. Addition of more barium hydroxide solution (60 c.c.) to the mother-liquors precipitated a further quantity of barium salt which was centrifuged and combined with the first lot. The combined barium salts were dissolved in water (60 c.c.), and carbon dioxide was passed through the solution. The small amount of insoluble material produced at this stage was removed by centrifugation, and the crude barium salt of (I; R = CH_2Ph, R′ = PO_3H_2, R″ = H) precipitated by addition of alcohol, centrifuged, washed with alcohol and then ether, and dried at 100° (6·9 g., 75%) (Found : Ba, 35·6. Calc. for $C_{16}H_{22}O_8NPBa$: Ba, 26·1%). Barium was removed from the barium salt (5·7 g.) in water (100 c.c.) by dilute sulphuric acid (rhodizonic acid indicator), and the sulphate was separated by centrifugation and washed twice with cold water. Combined washings and supernatant liquor were diluted with alcohol (100 c.c.) and hydrogenated at room temperature and atmospheric pressure with a palladium oxide catalyst. When hydrogen absorption had ceased the catalyst was filtered off and barium hydroxide solution added to pH 8. After evaporation of the solution to about 40 c.c. under reduced pressure, alcohol (150 c.c.) was added and the precipitated barium salt collected by centrifugation. This was redissolved in water (50 c.c.), a small amount of insoluble material removed by centrifugation, and the barium salt reprecipitated by alcohol.

It was collected, washed with alcohol and ether, and dried as before (5·0 g.). Further purification was effected by dissolution in the minimum quantity of cold water, heating to 100°, filtering from some precipitated barium salts (all the barium salts described in this paper are more soluble in cold than in hot water), and addition of alcohol to the filtrate to precipitate the purified material. Repetition of this process yielded a pure *barium* salt (Found : C, 21·7; H, 3·6; N, 2·4; P, 6·5. $C_9H_{15}O_8NPBa_{1\cdot5}$ requires C, 21·5; H, 3·0; N, 2·8; P, 6·2%).

(±)-2-*Benzyloxy*-3 : 3-*dimethylbutyro*-γ-*lactone* (V).—Pantolactone (11·8 g.) was added to a solution of sodium (2·09 g.) in dry alcohol (30 c.c.), and the solvent removed by distillation under reduced pressure. The solid sodio-derivative of pantolactone was dried at 90°/0·2 mm. and powdered under dry xylene (30 c.c.), and the suspension boiled under reflux with benzyl chloride (11·5 g.) for 2 hours. The cooled solution was washed with sulphuric acid (20 c.c.; 2N.) and then water, and dried (Na_2SO_4), and solvent removed by distillation at reduced pressure. The residual oil yielded on distillation the *benzyl ether* (14·5 g., 72%), b. p. 100—110°/10^{-3} mm. or 80°/10^{-4} mm. in a short-path still, as a crystalline solid, m. p. 46—47° (Found : C, 70·9; H, 7·4. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%). When heated for 5 minutes at 80° the ether (0·2115 g.) consumed the expected amount of sodium hydroxide (1·05 ml.; 0·911N.). Acidification of the resulting solution with hydrochloric acid precipitated the benzyl ether as an oil which was extracted with ether. The ethereal solution, dried (Na_2SO_4) and evaporated, left an oil which crystallised when seeded and rubbed (0·19 g., 90%), m. p. 46—47°, undepressed on admixture with an authentic sample of the benzyl ether, m. p. 46—47°.

(±)-*Pantothenic Acid* 2′-*Benzyl Ether* (I; R = R″ = H, R′ = CH_2Ph).—The sodium salt (0·44 g.) of β-alanine and kieselguhr (0·5 g.) were ground together and the intimate mixture was dried over phosphoric oxide. The benzyl ether (V) (0·88 g.) was added and the mixture heated at 120° for 2 hours. The pasty mass which solidified on cooling was triturated with ether and water and filtered from silica. The ethereal layer, on evaporation, yielded unchanged benzyl ether (0·12 g.). The aqueous layer was acidified to Congo-red with hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water, dried (Na_2SO_4), and evaporated. The slightly impure (±)-*pantothenic acid* 2′-*benzyl ether* remained as a pale yellow syrup (1·05 g., 85%) (Found : N, 4·3. $C_{16}H_{23}O_5N$ requires N, 4·5%) (0·513 g. required 1·63 ml. of N-sodium hydroxide for neutralisation to phenolphthalein. Calc.: 1·66 ml.). Hydrogenation of a sample dissolved in alcohol at room temperature and atmospheric pressure with a

palladium catalyst yielded pantothenic acid, identified as its benzylthiuronium salt, m. p. 132—133°, undepressed on admixture with an authentic sample.

Pantothenic Acid 4′-Phosphate (I; R = R′ = H, R″ = PO_3H_2).—Diphenyl chlorophosphonate (3·1 g., 1·1 mols.) in anhydrous pyridine (8 c.c.) was added dropwise to a solution of pantothenic acid 2′-benzyl ether (3·25 g., 1 mol.) in pyridine (10 c.c.) cooled to −10°. The mixture was kept at −10° for 1 hour and left at room temperature overnight. Water (*ca.* 1 c.c.) was added and as much pyridine as possible removed by distillation under reduced pressure. The residue was dissolved in chloroform, washed with water (15 c.c.), dilute hydrochloric acid (15 c.c.), and finally water (3 × 15 c.c.), and then dried (Na_2SO_4). Evaporation of the chloroform left a viscous, pale yellow syrup (5·45 g.). Attempts to prepare a *S*-benzylthiuronium salt from a sample of this material were unsuccessful, the only crystalline Product isolated being a small amount of the *S*-benzylthiuronium salt of diphenyl phosphate, m. p. 195—197°, undepressed when mixed with a sample of the authentic salt prepared by the method described below. The syrup without further purification was hydrogenated in acetic acid solution at room temperature and atmospheric pressure with a platinum oxide catalyst. When hydrogen absorption had ceased, barium acetate (4·0 g.) dissolved in the minimum amount of water was added and solvent removed by distillation under reduced pressure. The residue was dissolved in water and the pH adjusted to 8—9 by saturated barium hydroxide solution. A small precipitate of barium phosphate was centrifuged off and barium removed quantitatively from the clear supernatant liquid by titration with sulphuric acid (rhodizonic acid). Barium sulphate was removed by centrifugation and the volume of the supernatant liquid concentrated under reduced pressure. Barium hydroxide was added again to pH 8 and the crude phosphate precipitated by acetone, washed with acetone and then ether, and dried at 100° (yield, 3·9 g., 82%) (Found : C, 23·2; H, 4·2; N, 2·8. Calc. for $C_9H_{15}O_8NPBa_{1\cdot5}$: C, 21·5; H, 3·0; N, 2·8%).

Purification via *the lead salt.* The barium salt (1·0 g.) was dissolved in water (*ca.* 5 c.c.), and a saturated solution of lead acetate added until precipitation was complete. The heavy white precipitate was centrifuged and washed with a little cold water, in which it was appreciably soluble. The precipitate was re-suspended in water, lead removed by precipitation as the sulphide which was centrifuged off, and the clear solution reduced slightly in volume under reduced pressure. Barium hydroxide solution was added to pH 9 and the slight excess of alkali removed by carbon dioxide and centrifugation. The clear solution, on dilution with alcohol, yielded the pure *barium* salt (0·45 g.) which was washed with alcohol and ether and dried in a desiccator (Found : C, 22·0; H, 3·2; N, 3·0; P, 5·8; Ba, 41·5. $C_9H_{15}O_8NPBa_{1\cdot5}$ requires C, 21·5; H, 3·0; N, 2·8; P, 6·2; Ba, 41·1%).

Benzyl Pantothenate 2′-Benzyl Ether (I; R = R′ = CH_2Ph, R″ = H).—β-Alanine benzyl ester (5·3 g.) and (V) (6·5 g.) were heated together at 100° for 3 hours, then cooled, and the oily product dissolved in ether and washed with water. After being dried ($MgSO_4$) the solvent was removed under reduced pressure, yielding *benzyl pantothenate 2′-benzyl ether* as a viscous oil (10·7 g., 90%) (Found : C, 68·9; H, 7·4; N, 3·2. $C_{33}H_{39}O_5N$ requires C, 69·2; H, 7·3; N, 3·5%).

Phosphorylation.—Diphenyl chlorophosphonate (10 g., 1·5 mols.) was added dropwise to a solution of the benzyl ester (9·85 g., 1 mol.) in anhydrous pyridine (30 c.c.) cooled to −10°. After the mixture had been kept at room temperature overnight, water (*ca.* 5 c.c.) was added and as much pyridine as possible removed by distillation under reduced pressure. The oily residue was dissolved in chloroform (30 c.c.), washed successively with hydrochloric acid (2N.), water, sodium hydrogen carbonate solution (2·5%), and water (30 c.c. of each), and then dried ($MgSO_4$). Removal of the solvent gave the *diphenyl phosphate ester* (I; R = R′ = CH_2Ph, R″ = PO_3Ph_2) as a golden-yellow mobile oil (10·8 g., 71%) (Found : C, 67·0; H, 6·4; N, 2·1. $C_{33}H_{34}O_7NP$ requires C, 68·3; H, 6·2; N, 2·3%. The low carbon content is possibly caused by contamination with a little chloroform).

The oil (2·1 g.) in pure dioxan (*ca.* 10 c.c.) was passed through a column of Raney nickel and alumina to remove catalyst poisons and coloured impurities. Water (*ca.* 5 c.c.) was added to the eluate which was then hydrogenated at room temperature and atmospheric pressure with a mixed palladium–platinum oxide catalyst. A total of 1080 ml. of hydrogen was absorbed at an average rate of about 1·5 ml./min. (Theor. for 8 mols. = 1330 ml.). The catalyst was filtered off, barium hydroxide solution added to pH 8, and the solution evaporated to small volume under reduced pressure. Alcohol was added and the precipitated barium salt centrifuged off, washed with alcohol and then ether, and dried at room temperature (0·75 g., 44%).

Purification via *the silver and barium salts.* The impure barium salt (0·37 g.) was dissolved in water (*ca.* 5 c.c.), and a concentrated aqueous solution of silver nitrate (0·35 g.) added. The precipitated silver salt was centrifuged off, washed with a little water, suspended in water, and decomposed with hydrogen sulphide. Silver sulphide was centrifuged off and washed with water, and the combined supernatant liquid and washings were freed from hydrogen sulphide by evaporation under reduced pressure. Barium hydroxide solution was added to pH 9, carbon dioxide passed through the solution to remove excess of barium ions, and a small precipitate of barium carbonate centrifuged off. The clear aqueous solution was diluted with alcohol and the precipitated barium salt removed by centrifugation. Final purification was effected by redissolving the salt in water, centrifuging off a small precipitate, and precipitating the product with alcohol. The pure *salt* (0·22 g.) was washed with alcohol and ether and dried at 100°/0·1 mm. (Found : C, 21·3; H, 3·7; N, 2·8; P, 5·9; Ba, 40·8. $C_9H_{15}O_8NPBa_{1\cdot5}$ requires C, 31·5; H, 3·0; N, 2·8; P, 6·2; Ba, 41·1%). A sample of the solution of barium salt obtained directly from the silver salt was evaporated to dryness from the frozen state but analysis indicated that this was not pure.

S-*Benzylthiuronium Salts of Diphenyl and Dibenzyl Phosphate.*—Prepared from the corresponding sodium salts and benzylthiuronium chloride in aqueous alcohol in the usual way and recrystallised from aqueous alcohol, S-*benzylthiuronium diphenyl phosphate* crystallised as needles, m. p. 195—197° (Found : C, 57·8; H, 5·4; N, 6·5; S, 7·4. $C_{20}H_{21}O_4N_2PS$ requires C, 57·7; H, 5·1; N, 6·7; S, 7·7%), and

S-benzylthiuronium dibenzyl phosphate as fine silky needles, m. p. 163—164° (Found: C, 59·3; H, 5·5; N, 6·0; S, 6·8. $C_{22}H_{25}O_4N_2PS$ requires C, 59·5; H, 5·6; N, 6·3; S, 7·2%).

Acid Hydrolysis of Pantothenic Acid 2'- and 4'-Phosphate and Pantolactone 2-Phosphate.—The barium salts of pantothenic acid 2'- and 4'-phosphate (*ca.* 6 mg.) and of pantolactone 2-phosphate (*ca.* 3 mg.) were severally dissolved in hydrochloric acid (20 ml.; 2N.), and the solutions heated in hard glass flasks in a boiling water-bath. Free phosphate was measured in aliquots at intervals photometrically by the method of Allen (*Biochem. J.*, 1940, **34**, 858), with the following results:

Time (mins.)	30	60	105	160	255	335	400
Free phosphorus, %: 2'-ester	2·4	6·0	6·8	9·7	18·4	20·8	21·8
4'-ester	10·1	25·1	40·2	55·9	63·0	67·0	—
lactone 2-phosphate	4·4	6·0	8·4	9·3	17·2	19·9	20·8

Alkaline Hydrolysis.—The barium salts (*ca.* 6 mg.) were severally dissolved in water (2—3 c.c.), and a slight excess of sodium sulphate was added to precipitate barium as its sulphate. The precipitates were centrifuged off and washed with water. Supernatant liquids and washings were made up to 20 ml. with sodium hydroxide solution so that the final concentration was 0·5N. The alkaline solutions were heated at 100° in silver tubes, and aliquots withdrawn at intervals. Free phosphate was determined as above. After 2 hours there was no measurable phosphate liberated from either pantothenic acid 2'- or 4'-phosphate.

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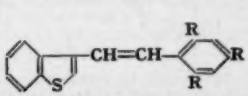
58. *Thiophen Derivatives of Potential Biological Interest. Part II. Thionaphthen Analogues of Stilbene and Related Compounds.*

By NG. PH. BUU-HOÏ and NG. HOÁN.

Numerous new derivatives of thionaphthen akin to stilbene and to αβ-diphenylacrylonitrile have been prepared by known methods for biological investigation; some contain another polycyclic radical in addition to the thionaphthen nucleus. During this work the properties of several thionaphthen aldehydes and ketones and of 3-thionaphthenylacetonitrile have been examined.

SUBSTANCES of structure analogous to stilbene and bearing one or more polycyclic radicals are of interest in connection with a recent theory concerning the mode of action of carcinogens (Pinck, *Ann. New York Acad. Sci.*, 1948, **50**, 1). According to this theory, the action of tumour-producing substances, especially those with methyl or methylene groups, may involve biochemical conversion into ethylenic compounds and subsequent intervention of their external double bonds in chain reactions with certain cellular constituents.

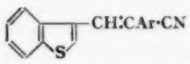
A consequence of this theory is that more ethylenic compounds should be tested for carcinogenic properties; it is of interest in this respect that β-*sec.*-butyl-α-ethylstilbene has already been found to be carcinogenic (Dodds, *Brit. Med. Bull.*, 1947, **4**, 972). The present paper deals mainly with the preparation of substances akin to stilbene and containing the thionaphthen nucleus. The two thionaphthen intermediates used in this work were 3-formylthionaphthen (I; R = CHO), conveniently prepared by King and Nord's method (*J. Org. Chem.*, 1948, **13**, 635), and 3-thionaphthenylacetonitrile (I; R = CH_2·CN) (Avakian, Moss, and Martin, *J. Amer. Chem. Soc.*, 1948, **70**, 3075); 3-chloromethylthionaphthen (I; R = CH_2Cl), required for their preparation, was obtained by chloromethylation of thionaphthen according to the Darzens–Levy procedure (*Compt. rend.*, 1936, **202**, 73), which gave also a liquid unidentified dithionaphthenylmethane.

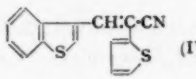
(I.)  (II.)

Reaction of 3-formylthionaphthen with benzylmagnesium chloride, followed by dehydration of the secondary alcohol thus formed, gave a liquid 3-styrylthionaphthen (II; R = H); reaction of the same aldehyde with 2 : 4 : 6-trinitrotoluene in the presence of piperidine, a procedure used in the aromatic series by Pfeiffer and Monath (*Ber.*, 1906, **39**, 1306), gave 3-(2 : 4 : 6-trinitrostyryl)thionaphthen (II; R = NO_2).

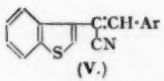
Another route to analogues of stilbene was the condensation of 3-formylthionaphthen in the presence of alkaline catalysts with arylacetonitriles. A series of α-aryl-β-3-thionaphthenylacrylonitriles (III) was thus easily prepared (see Table I); when 2-thienylacetonitrile was used in the latter process, α-2-thienyl-β-3-thionaphthenylacrylonitrile (IV) was obtained. Analogous condensation of various aromatic aldehydes with 3-thionaphthenylacetonitrile yielded a series of β-aryl-α-3-thionaphthenylacrylonitriles (V), listed in Table II along with a number of β-2-thienyl-α-3-thionaphthenylacrylonitriles of types (VI) and (VII) obtained similarly with various thiophen aldehydes. Mention should particularly be made of β-9-anthryl- (VIII) and β-3-pyrenyl-α-3-thionaphthenylacrylonitrile (IX), which represent highly condensed stilbene-like compounds, in the line of those postulated by Pinck (*loc. cit.*) as having a likelihood of carcinogenicity.

It is worth mention that, although β-*p*-methoxyphenyl-α-3-thionaphthenylacrylonitrile (as V) was readily demethylated by pyridine hydrochloride to the corresponding *p*-hydroxyphenyl compound, the *o*-methoxy-nitrile was converted by the same reagent into 3-3′-thionaphthenylcoumarin (X; R = H); 6-chloro- (X; R = Cl) and 6-bromo-3-3′-thionaphthenylcoumarin (X; R = Br) were also similarly prepared from β-(5-chloro-2-methoxyphenyl)- and β-(5-bromo-2-methoxyphenyl)-α-3′-thionaphthenylacrylonitrile. In the 5 : 6-benzocoumarin series, the compound (XI) could also be obtained from β-(2-methoxy-1-naphthyl)-α-3-thionaphthenylacrylonitrile in the same way. This confirms earlier observations on the formation of similar compounds in the aromatic and thiophen series (Buu-Hoï, Hoán, and Lavit, *J.*, 1950, 2130).

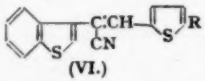
(III.) 



(IV.)



(V.)



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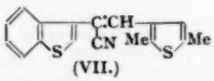
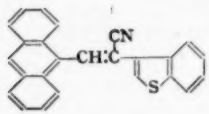
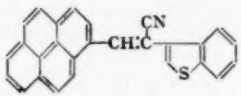
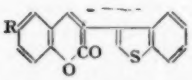


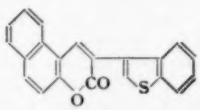
(VII.)

(VIII.) 



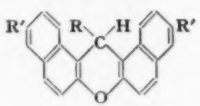
(IX.)

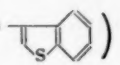
(X.) 

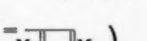


(XI.)

The ready accessibility of 3-formylthionaphthen by the Sommelet method led us to investigate its properties further. Nitration under conditions in which thiophen derivatives are attacked in the 2-position gave a single product, apparently 3-formyl-2-nitrothionaphthen. This reaction could be generalised to 3-acylthionaphthens, and 3-acetyl-2-nitro-, 2-nitro-3-propionyl-, and 3-*n*-butyryl-2-nitro-thionaphthen were thus readily obtained. 3-Thionaphthenylacetontrile gave no definite compound on nitration, but yielded easily an azomethine with 4-nitrosodimethylaniline.



(XII; R′ = H, XIII; R′ = Br,) R = 

(XIV; R′ = H, R = )

As in the case of aromatic aldehydes (Claisen, *Annalen*, 1887, **237**, 270), 3-formylthionaphthen readily condensed with β-naphthol in the presence of mineral acid to give 5-3′-thionaphthenyl-3 : 4-6 : 7-dibenzoxanthen (XII); with 6-bromo-2-naphthol, the 2′ : 3″-dibromo-compound (XIII) was similarly obtained. This behaviour distinguishes 3-formylthionaphthen from

2-formylthiophen, which under the same conditions gave coal-like compounds, and relates it to 3-formyl-2 : 5-dimethylthiophen, which also readily gave 5-(2 : 5-dimethyl-3-thienyl)-3 : 4-6 : 7-dibenzoxanthen (XIV).

Experimental.

Preparation of Intermediates.—3-Chloromethylthionaphthen, prepared by the Darzens–Levy method (King and Nord, *loc. cit.*), was best isolated by dilution with water of the acetic acid medium containing the reaction product, and extraction by means of benzene, a solvent which does not take up acetic acid appreciably in the presence of water. The benzene solution was washed with dilute aqueous sodium hydrogen carbonate and dried (Na_2SO_4), the solvent removed in a vacuum, and the residue vacuum-distilled. After repeated recrystallisation from ligroin, it had m. p. 42° (lit., m. p. 39—40°). The higher-boiling by-products (b. p. 250—300°/13 mm.) crystallised partly. The solid removed had m. p. 216° after recrystallisation from ethanol, and its constitution is being investigated. The liquid part gave on redistillation a pale yellow viscous oil, b. p. 280—282°/13 mm., probably a *dithionaphthenylmethane* (Found : C, 72·4; H, 4·5. $C_{17}H_{12}S_2$ requires C, 72·9; H, 4·3%).

3-*Styrylthionaphthen.*—A solution of 3-formylthionaphthen (5 g.) in anhydrous ether (10 c.c.) was added in small portions to a cooled Grignard solution [from magnesium (1·8 g.) and benzyl chloride (10 g.) in ether (60 c.c.)]. A mixture of the crude carbinol thus obtained and 98% formic acid (20 c.c.) was refluxed for 5 minutes, then poured into water, and the styryl compound taken up in benzene and purified by vacuum-fractionation. It formed a pale yellow viscous oil, b. p. 238—242°/13 mm. (4·5 g.), which did not solidify even after prolonged storage and gave with sulphuric acid a dark green colour. This substance was apparently a mixture of the two possible stereoisomers of 3-styrylthionaphthen (Found : C, 81·0; H, 5·3. Calc. for $C_{16}H_{12}S$: C, 81·35; H, 5·1%).

3-(2 : 4 : 6-*Trinitrostyryl*)*thionaphthen.*—This *compound* was obtained in quantitative yield by refluxing a solution of 2 : 4 : 6-trinitrotoluene (1 g.) and 3-formylthionaphthen (1 g.) in dry benzene (10 c.c.) for 3 hours with 2 drops of piperidine; it formed, from ethanol, fine orange-red needles, m. p. 182°, giving with hot sulphuric acid a blue-violet colour (Found : N, 11·2. $C_{16}H_9O_6N_3S$ requires N, 11·3%).

Preparation of Acrylonitriles of Types (III), (IV), (V), (VI), *and* (VII).—Most of these were prepared by shaking a mixture of the aldehyde and the arylacetonitrile in warm ethanol with a few drops of 30% aqueous potassium hydroxide; the substances obtained were recrystallised from ethanol. In the case of *p*-nitrophenylacetonitrile, the alkaline catalyst was piperidine. *p*-Fluoro-, *p*-chloro-, and *p*-bromophenylacetontrile were best prepared by chloromethylation of fluoro-, chloro-, and bromo-benzene, and treatment of the corresponding chloromethyl compounds with sodium cyanide in ethanol–water. α- and β-Naphthylacetonitrile were best prepared from α- and β-methylnaphthalene by side-chain bromination with *N*-bromosuccinimide (Buu-Hoï, *Annalen*, 1944, **556**, 1), and subsequent treatment with sodium cyanide; 2-methoxy-1-naphthylacetonitrile (b. p. 230—235°/18 mm.) was similarly prepared from 1-chloromethyl-2-methoxynaphthalene (Badger, Carruthers, and Cook, *J.*, 1949, 1678). 2-Methoxy-1-naphthaldehyde, 3-formylacenaphthene, 9-anthraldehyde, 3-formylpyrene, and the thiophen aldehydes were prepared by the *N*-methylformanilide method. Demethylation of acrylontriles bearing methoxy-groups was effected in the usual way by refluxing the required methoxy-compound (1 part) with redistilled pyridine hydrochloride; after dilution with water, the precipitate formed was collected, washed with water, dried, and crystallised from benzene.

The *products* obtained are reported in Tables I and II.

3-3′-*Thionaphthenylcoumarin* (X; R = H).—A mixture of β-*o*-methoxyphenyl-α-3-thionaphthenylacrylontrile (1 g.) and pyridine hydrochloride (5 g.) was refluxed for 15 minutes. After dilution with water, the precipitate (1 g.) was collected, washed thoroughly with water, dried, and recrystallised from benzene; fine yellowish needles, m. p. 181°, insoluble in aqueous sodium hydroxide, were thus obtained (Found : C, 73·1; H, 3·5. $C_{17}H_{10}O_2S$ requires C, 73·4; H, 3·6%).

6-*Bromo*-3-3′-*thionaphthenylcoumarin* (X; R = Br) was similarly obtained from β-(5-bromo-2-methoxyphenyl)-α-3-thionaphthenylacrylonitrile, and formed from benzene a yellowish microcrystalline powder, m. p. 223° (Found : C, 56·7; H, 2·8. $C_{17}H_9O_2SBr$ requires C, 57·1; H, 2·5%). The 6-chloro-compound was obtained similarly in an impure state and had m. p. 175—180°.

3-3′-*Thionaphthenyl*-5 : 6-*benzocoumarin* (XI) crystallised from ethanol–benzene as fine shiny yellow needles, m. p. 222° (Found : C, 76·5; H, 3·6. $C_{21}H_{12}O_2S$ requires C, 76·8; H, 3·7%).

α-p-*Dimethylaminoanilo*-α-3-*thionaphthenylacetonitrile.*—A solution of *p*-nitrosodimethylaniline (0·5 g.) and 3-thionaphthenylacetonitrile (0·9 g.) in ethanol was treated with 2 drops of a concentrated solution of potassium hydroxide in ethanol. The precipitate of *anilo*-derivative obtained formed, from ethanol, fine violet-red prisms, m. p. 164° (Found : N, 13·4. $C_{18}H_{15}N_3S$ requires N, 13·7%).

5-3′-*Thionaphthenyl*-3 : 4-6 : 7-*dibenzoxanthen* (XII).—A solution of β-naphthol (2 g.) and 3-formylthionaphthen (1 g.) in boiling acetic acid (20 c.c.) was treated with a few drops of concentrated hydrochloric acid. The dark oil formed solidified after cooling; after repeated crystallisation from acetic acid, colourless needles, m. p. 280°, of the *dibenzoxanthen* were obtained (Found : C, 83·6; H, 4·2. $C_{29}H_{16}OS$ requires C, 84·0; H, 4·3%).

2′ : 3″-*Dibromo*-5-3′-*thionaphthenyl*-3 : 4-6 : 7-*dibenzoxanthen.*—Similarly obtained from 6-bromo-2-naphthol (3·2 g.) and 3-formylthionaphthen (1 g.), this *compound* formed, from acetic acid, fine colourless needles, m. p. 325° (Found : C, 60·5; H, 2·9. $C_{29}H_{14}OSBr_2$ requires C, 60·8; H, 2·8%).

5-(2 : 5-*Dimethyl*-3-*thienyl*)-3 : 4-6 : 7-*dibenzoxanthen* (XIV).—This *dibenzoxanthen*, prepared from 2 : 5-dimethyl-3-formylthiophen (1 g.) and β-naphthol (2 g.), formed colourless prisms, m. p. 225°, from acetic acid (Found : C, 82·4; H, 5·2. $C_{27}H_{20}OS$ requires C, 82·6; H, 5·1%).

3-*Formyl*-2-*nitrothionaphthen*.—To a well-stirred, ice-cooled solution of 3-formylthionaphthen (9 g.) in acetic anhydride (50 c.c.), a mixture of fuming nitric acid (*d* 1·49) and acetic acid (40 c.c.) was added dropwise. After 15 minutes, the reaction product was poured on cracked ice; the precipitate formed after some hours was collected, thoroughly washed with water, and recrystallised from ethanol, giving pale yellow needles (7 g.), m. p. 124° (Found : C, 51·9; H, 2·5. $C_9H_5O_3NS$ requires C, 52·1; H, 2·4%).

TABLE I.

Acrylonitriles (III) *and* (IV).

			Found, %.		Reqd., %.	
β-3-Thionaphthenylacrylonitrile.[a]	M. p.	Formula.	C.	H.	C.	H.
α-Phenyl-	132°	$C_{17}H_{11}NS$	78·0	4·3	78·2	4·2
α-*p*-Tolyl-	139	$C_{18}H_{13}NS$	78·5	4·8	78·5	4·7
α-*p*-Ethylphenyl-	115	$C_{19}H_{15}NS$	78·6	5·4	78·9	5·2
α-*p*-Chlorophenyl-	180	$C_{17}H_{10}NSCl$	68·9	3·7	69·0	3·4
α-*p*-Bromophenyl-	175	$C_{17}H_{10}NSBr$	59·8	2·9	60·0	2·9
α-*p*-Methoxyphenyl-	118	$C_{18}H_{13}NOS$	74·0	4·8	74·2	4·5
α-*p*-Hydroxyphenyl-	202	$C_{17}H_{11}NOS$	73·2	4·0	73·6	4·0
α-*p*-Nitrophenyl-[b]	209	$C_{17}H_{10}N_2O_2S$	66·5	3·0	66·7	3·3
α-1-Naphthyl-	144	$C_{21}H_{13}NS$	80·9	4·4	81·0	4·2
α-2-Naphthyl-	179	$C_{21}H_{13}NS$	81·0	4·2	81·0	4·2
α-(2-Methoxy-1-naphthyl)-	147	$C_{22}H_{15}ONS$	77·6	4·6	77·4	4·4
α-2-Thienyl-	105	$C_{15}H_9NS_2$	67·3	3·5	67·4	3·4
α-3-Thionaphthenyl-	203	$C_{19}H_{11}NS_2$	71·8	3·8	71·9	3·5

[a] All shiny yellow needles, unless otherwise stated; all gave with sulphuric acid halochromic colours ranging from yellow to brown. [b] Orange.

TABLE II.

Acrylonitriles (V), (VI), *and* (VII).

			Found, %.		Reqd., %.	
α-3-Thionaphthenylacrylonitrile.[a]	M. p.	Formula.	C.	H.	C.	H.
β-Phenyl-	114°	$C_{17}H_{11}NS$	78·2	4·4	78·2	4·2
β-*p*-Chlorophenyl-	146	$C_{17}H_{10}NClS$	68·9	3·6	69·0	3·3
β-*m*-Nitrophenyl-	150	$C_{17}H_{10}O_2N_2S$	66·6	3·5	66·7	3·3
β-*p*-Fluorophenyl-	154	$C_{17}H_{10}NFS$	72·8	3·8	73·1	3·6
β-*o*-Methoxyphenyl-	125	$C_{18}H_{13}ONS$	74·4	4·4	74·6	4·5
β-*p*-Methoxyphenyl-	97	$C_{18}H_{13}ONS$	74·4	4·6	74·6	4·5
β-*p*-Hydroxyphenyl-	184	$C_{17}H_{11}ONS$	73·3	4·0	73·6	4·0
β-3 : 4-Dichlorophenyl-	153	$C_{17}H_9NCl_2S$	61·8	2·9	61·8	2·7
β-2 : 4-Dichlorophenyl-	142	$C_{17}H_9NCl_2S$	61·6	2·8	61·8	2·7
β-3 : 4-Dimethoxyphenyl-	143	$C_{19}H_{15}O_2NS$	70·8	4·7	71·0	4·6
β-3 : 4-Dihydroxyphenyl-	155	$C_{17}H_{11}O_2NS$	69·6	3·8	69·6	3·7
β-(5-Chloro-2-methoxyphenyl)-	146	$C_{18}H_{12}ONClS$	65·6	3·8	65·9	3·6
β-(5-Bromo-2-methoxyphenyl)-	164	$C_{18}H_{12}ONBrS$	58·6	3·5	58·4	3·2
β-1-Naphthyl-	138	$C_{21}H_{13}NS$	80·9	4·4	81·0	4·2
β-2-Naphthyl-	148	$C_{21}H_{13}NS$	80·8	4·4	81·0	4·2
β-3-Acenaphthenyl-[b]	176	$C_{23}H_{15}NS$	81·9	4·5	81·9	4·4
β-9-Anthryl-[b]	220	$C_{25}H_{15}NS$	83·2	4·0	83·1	4·1
β-3-Pyrenyl-[b]	231	$C_{27}H_{15}ONS$	84·0	3·8	84·2	3·9
β-2-Furyl-	94	$C_{15}H_9ONS$	71·4	3·4	71·7	3·6
β-2-Thienyl-	124	$C_{15}H_9NS_2$	67·3	3·5	67·4	3·4
β-(5-Methyl-2-thienyl)-	134	$C_{16}H_{11}NS_2$	68·0	3·6	68·0	3·9
β-(2 : 5-Dimethyl-3-thienyl)-	123	$C_{17}H_{13}NS_2$	69·8	4·4	69·9	4·2
β-(5-Chloro-2-thienyl)-	185	$C_{15}H_8NClS_2$	59·6	2·8	59·6	2·6
β-(5-Bromo-2-thienyl)-	183	$C_{15}H_8NBrS_2$	51·6	2·5	52·0	2·3
β-3 : 4-Dioxymethylenephenyl-	112	$C_{19}H_{11}O_2NS$	70·5	3·6	70·8	3·6
β-(2-Methoxy-1-naphthyl)-	151	$C_{22}H_{15}ONS$	77·0	4·6	77·4	4·4

[a] Yellow needles unless otherwise stated. All gave with sulphuric acid a colour ranging from yellow to violet; the hydroxy-compounds dissolved in aqueous sodium hydroxide to give yellow solutions. [b] Orange.

Nitration of 3-*Acylthionaphthens*.—This was effected as for the aldehyde; 3-acetyl-, 3-propionyl-, and 3-*n*-butyryl-thionaphthen were prepared according to Buu-Hoï and Cagniant (*Rec. Trav. chim.*, 1948, **67**, 64). Crystallisation of the products from ethanol gave 3-*acetyl*-2-*nitrothionaphthen*, fine yellow prisms, m. p. 179° (Found : C, 54·0; H, 3·0. $C_{10}H_7O_3NS$ requires C, 54·3; H, 3·1%) (with bromine in chloroform this gave a substitution product, m. p. 192°), 2-*nitro*-3-*propionylthionaphthen*, pale yellow

prisms, m. p. 145° (Found : C, 56·0; H, 4·0. $C_{11}H_9O_2NS$ requires C, 56·1; H, 3·8%), and 3-n-*butyryl*-2-*nitrothionaphthen*, long pale yellow needles, m. p. 107° (Found : C, 57·6; H, 4·7. $C_{12}H_{11}O_2NS$ requires C, 57·8; H, 4·4%).

3-p-*Anisoylthionaphthen*.—In connection with the study of thionaphthenyl ketones, 3-*p*-anisoylthionaphthen was prepared from thionaphthen (15 g.), anisoyl chloride (21 g.), and aluminium chloride (17 g.) in carbon disulphide (150 c.c.). The ketone (20 g.) formed, from ethanol, yellowish prisms, m. p. 112°, b. p. 275—285°/13 mm., giving a yellow colour in sulphuric acid (Found : C, 71·4; H, 4·6. $C_{16}H_{12}O_2S$ requires C, 71·6; H, 4·5%). Demethylation by means of pyridine hydrochloride in the usual way gave 3-p-*hydroxybenzoylthionaphthen*, crystallising from benzene in almost colourless needles, m. p. 185—187°, giving yellow solutions in alkali (Found : C, 70·5; H, 4·0. $C_{15}H_{10}O_2S$ requires C, 70·8; H, 3·9%).

Department of Organic Chemistry, The Radium Institute, University of Paris.

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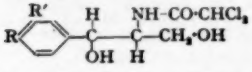
59. *Three New Analogues of Chloramphenicol.*

By Ng. Ph. Buu-Hoï, Ng. D. Xuong, and Ng. H. Khoï.

In continuation of our work on the relation between constitution and antibiotic activity in the chloramphenicol series, three further analogues of chloramphenicol have been synthesised for biological testing.

As has been reported recently, the antibacterial properties of chloramphenicol (chloromycetin) are qualitatively more connected with the *threo*-configuration of the molecule and the presence of a *p*-substituent in the phenyl nucleus than with the nature of that substituent (Buu-Hoï and Khoï, *Compt. rend.*, 1949, **229**, 1343; 1950, **230**, 967; Buu-Hoï, Hoán, Jacquignon, and Khoï, *ibid.*, 1950, **230**, 662; *J.*, 1950, 2766). In view of these results, three further substances having a molecular configuration akin to that of chloramphenicol (I), namely, *threo*-2-dichloroacetamido-1-*p*-tolyl- (II), -1-*p*-methoxyphenyl- (III), and -1-(3 : 4-dichlorophenyl)-propane-1 : 3-diol (IV), have now been prepared for biological testing. The method used



(I) : R = NO_2, R′ = H (III) : R = OMe, R′ = H.

(II) : R = Me, R′ = H. (IV) : R = R′ = Cl.

started from *p*-methyl-, *p*-methoxy-, and 3 : 4-dichloro-acetophenone, and followed the pattern frequently described (Long and Troutman, *J. Amer. Chem. Soc.*, 1949, **71**, 2469; Buu-Hoï *et al.*, *locc. cit.*). It is to be noted that in the condensation of formaldehyde with ω-acetamido-*p*-methyl- and -3 : 4-dichloro-acetophenone, the introduction of only one hydroxymethyl group was again observed; another feature of the present syntheses was the formation of a single secondary alcohol (believed by reason of analogy to be the *threo*-compound) in the Ponndorf–Meerwein reduction of ω-acetamido-β-hydroxy-*p*-methyl-, α-acetamido-β-hydroxy-*p*-methoxy-, and ω-acetamido-3 : 4-dichloro-β-hydroxy-propiophenone.

Screening bacteriological tests showed compounds (II) and (III) to have an extremely low degree of activity against *Escherichia coli* and *Staphylococcus aureus*. Compound (III) showed notable activity against *Shigella paradysenteriae* and *St. aureus*.

Experimental.

Preparation of Intermediates.—The large-scale preparation of 4-methyl- and 4-methoxy-acetophenone presented no difficulty, but that of 3 : 4-dichloroacetophenone according to the method described in the literature (Roberts and Turner, *J.*, 1927, 1855) gave extremely low yields, and another method was devised. Into a well-stirred mixture of *o*-dichlorobenzene (400 c.c.) and powdered aluminium chloride (300 g.) kept at 80°, acetic anhydride (150 g.) was dropped during 1 hour. Stirring was continued for 3 more hours, during which the temperature was raised to 120°. After 6 hours at room temperature, the semi-solid reaction mixture was treated with ice and hydrochloric acid, and the ketone thus obtained (128 g.) purified by vacuum-distillation; after recrystallisation from ligroin, it had m. p. 76°.

ω-*Acetamido*-4-*methylacetophenone*.—The hexamethylenetetramine salt of ω-bromo-4-methylacetophenone (170 g.) was prepared from ω-bromo-4-methylacetophenone (130 g.) (Kunckell, *Ber.*, 1897, **30**, 577) and hexamethylenetetramine (94 g.) in chlorobenzene (200 c.c.) in the usual way, and formed colourless microcrystals, m. p. 188° (decomp.). Hydrolysis by means of hydrochloric acid (250 c.c.) in ethanol (400 c.c.) gave α-amino-4-methylacetophenone hydrochloride (86 g.), m. p. 220° (decomp.);

Ryan (Ber., 1898, **31**, 2133) gave m. p. 206° for a product prepared by another method. To a well-stirred solution of this salt (120 g.) in ice-water (550 g.), acetic anhydride (150 g.) and then a solution of sodium acetate (175 g.) in ice-water (100 g.) were cautiously added. After 1 more hour's stirring, the solid *ω-acetamido-4-methylacetophenone* was filtered off and recrystallised from ethyl acetate, giving fine colourless prisms, m. p. 132° (Found : N, 7·2. $C_{11}H_{13}O_2N$ requires N, 7·3%).

*α-Acetamido-β-hydroxy-*p*-methylpropiophenone.*—A mixture of the foregoing amide (19 g.), ethanol (70 c.c.), and 30% aqueous formaldehyde (40 c.c.) was stirred with pure sodium hydrogen carbonate (1 g.; prepared *in situ* from sodium carbonate and carbon dioxide) for 2 hours at 35°. The solution thus obtained was concentrated *in vacuo* and thoroughly extracted with ethyl acetate. The *ketone* obtained after evaporation of the solvent (16 g.) crystallised from ethyl acetate in fine colourless needles, m. p. 121°, very soluble in ethanol (Found : C, 65·0; H, 6·8. $C_{12}H_{15}O_3N$ requires C, 65·1; H, 6·7%).

DL-threo-2-*Acetamido*-1-p-*tolylpropane*-1 : 3-*diol.*—A solution of the foregoing compound (15 g.) and aluminium *iso*propoxide (21 g.) in anhydrous *iso*propyl alcohol (170 c.c.) was gently heated for 12 hours with removal of acetone; water (20 c.c.) was then added and the mixture boiled for some minutes. The solid formed was filtered off and thoroughly extracted with boiling *iso*propyl alcohol; the filtrate was combined with the extracts, and the whole concentrated *in vacuo*. The *diol* (7 g.) formed, from ethyl acetate or methanol, colourless lustrous leaflets, m. p. 150° (Found : C, 64·3; H, 7·7. $C_{12}H_{17}O_3N$ requires C, 64·5; H, 7·7%). No isomer could be detected in the mother-liquors.

DL-threo-2-*Amino*-1-p-*tolylpropane*-1 : 3-*diol.*—The foregoing amide (2 g.) was hydrolysed by 10% hydrochloric acid (33 c.c.) at 95° for 2 hours; after basification of the cooled mixture by means of sodium hydroxide, the precipitated *amine* was recrystallised from benzene, giving fine colourless prisms (1 g.), m. p. 90° (Found : N, 7·4. $C_{10}H_{15}O_2N$ requires N, 7·7%).

DL-threo-2-*Dichloroacetamido*-1-p-*tolylpropane*-1 : 3-*diol* (II).—This *amide*, obtained from the foregoing amine (2 g.; dried *in vacuo*) by 2 hours' refluxing with freshly distilled ethyl dichloroacetate (5 c.c.) and precipitation with ligroin, formed from benzene fine colourless leaflets, m. p. 106° (Found : C, 49·4; H, 5·2. $C_{12}H_{15}O_3NCl_2$ requires C, 49·3; H, 5·2%)

ω-Acetamido-p-*methoxyacetophenone.*—*ω*-Bromo-*p*-methoxyacetophenone (95 g.) was prepared in good yield by dropping a solution of bromine in acetic acid into a well-cooled solution of *p*-methoxyacetophenone in acetic acid; Kunckell and Scheven (*Ber.*, 1898, **31**, 173) made this compound by the Friedel–Crafts reaction between anisole and bromoacetyl bromide, and Boeseken, Hansen, and Bertram (*Rec. Trav. chim.*, 1916, **35**, 311) made it by passing bromine vapour in *p*-methoxyacetophenone dissolved in acetic acid. It gave with hexamethylenetetramine (68 g.) an *adduct* which was precipitated from chlorobenzene (100 c.c.) as a colourless microcrystalline powder (135 g.), m. p. 222°. This yielded on hydrolysis with hydrochloric acid (170 c.c.) in methanol (200 c.c.) *ω*-amino-*p*-methoxyacetophenone hydrochloride (66 g.) which was treated with 70 g. of acetic anhydride. *ω-Acetamido*-p-*methoxyacetophenone* (43 g.) formed, from ethyl acetate, lustrous colourless leaflets, m. p. 117° (Found : N, 6·5. $C_{11}H_{13}O_3N$ requires N, 6·7%).

*α-Acetamido-β-hydroxy-*p*-methoxypropiophenone.*—Prepared from the foregoing amide (21 g.), aqueous formaldehyde (40 c.c.), and sodium hydrogen carbonate (1 g.) in ethanol (70 c.c.), this *ketone* formed, from ethyl acetate, shiny colourless needles (10 g.), m. p. 158° (Found : C, 61·0; H, 6·4. $C_{12}H_{15}O_4N$ requires C, 60·8; H, 6·3%).

DL-threo-2-*Acetamido*-1-p-*methoxyphenylpropane*-1 : 3-*diol.*—Obtained from the foregoing ketone (9 g.), aluminium *iso*propoxide (10 g.), and *iso*propyl alcohol (60 c.c.) in the usual way, this *diol* crystallised from water in large colourless prisms (7 g.), m. p. 123° (Found : C, 60·5; H, 7·3. $C_{12}H_{17}O_4N$ requires C, 60·2; H, 7·1%).

DL-threo-2-*Amino*-1-p-*methoxyphenylpropane*-1 : 3-*diol.*—Hydrolysis of the foregoing amide (6 g.) with 20% hydrochloric acid (60 c.c.) gave, after basification, the free *amine* (3 g.), crystallising in lustrous colourless leaflets, m. p. 102°, from ethyl acetate (Found : N, 6·8. $C_{10}H_{15}O_3N$ requires N, 7·1%).

DL-threo-2-*Dichloroacetamido*-1-p-*methoxyphenylpropane*-1 : 3-*diol* (III).—This *compound* (1·5 g.), obtained from the foregoing amine (2 g.) and methyl dichloroacetate (3 g.), formed fine lustrous colourless leaflets, m. p. 91°, from benzene (Found : C, 47·3; H, 5·0. $C_{12}H_{15}O_4NCl_2$ requires C, 46·8; H, 4·8%).

ω-Bromo-3 : 4-*dichloroacetophenone.*—This compound has apparently been prepared by Lutz *et al.* (*J. Org. Chem.*, 1947, **12**, 617), but was not described. To a solution of 3 : 4-dichloroacetophenone (50 g.) in acetic acid (100 c.c.) containing 48% hydrobromic acid (1 c.c.), bromine (43 g. in 50 c.c. of acetic acid) was added dropwise during 2 hours. The precipitate obtained on decomposition of the reaction mixture with cracked ice crystallised from ethanol in fine shiny colourless needles (70 g.), m. p. 63°. The hexamethylenetetramine *adduct* (92 g.) obtained from the bromo-ketone (70 g.) and hexamethylenetetramine (41 g.) in chlorobenzene (100 c.c.) was obtained from this solvent as a colourless microcrystalline powder, m. p. 225° (decomp.) (Found : N, 13·3. $C_{14}H_{17}ON_4BrCl_2$ requires N, 13·7%).

ω-Acetamido-3 : 4-*dichloroacetophenone.*—The foregoing adduct (90 g.) was stirred with hydrochloric acid (200 c.c.) in methanol (150 c.c.) for 12 hours at room temperature, giving *ω-amino*-3 : 4-*dichloroacetophenone hydrochloride* in the form of fine colourless needles (50 g.), decomp. >300°; usual treatment of this salt (48 g.) with acetic anhydride (60 g.) and sodium acetate (50 g.) gave the *amide* which crystallised from ethyl acetate in long shiny colourless needles (45 g.), m. p. 137° (Found : N, 5·5. $C_{10}H_9O_2NCl_2$ requires N, 5·7%).

α-Acetamido-3 : 4-*dichloro-β-hydroxypropiophenone.*—Obtained from the foregoing substance (43 g.), aqueous formaldehyde (32 c.c.), and sodium hydrogen carbonate (2 g.) in ethanol (200 c.c.), this *compound* formed, from ethyl acetate and methanol, fine shiny colourless prisms (12 g.), m. p. 158° (Found : C, 47·9; H, 3·9; N, 4·7. $C_{11}H_{11}O_3NCl_2$ requires C, 47·8; H, 4·0; N, 5·0%).

DL-threo-2-*Acetamido*-1-(3 : 4-*dichlorophenyl*)*propane*-1 : 3-*diol*.—The reduction of the foregoing ketone (6 g.) with aluminium *iso*propoxide (5 g.) in *iso*propyl alcohol (30 c.c.) yielded a single *alcohol* crystallising from methanol in lustrous colourless leaflets (5 g.), m. p. 169° (Found : C, 47·5; H, 4·6. $C_{11}H_{13}O_3NCl_2$ requires C, 47·4; H, 4·6%).

DL-threo-2-*Amino*-1-(3 : 4-*dichlorophenyl*)*propane*-1 : 3-*diol* formed shiny colourless leaflets, m. p. 130°, from benzene (Found : N, 5·9. $C_9H_{11}O_2NCl_2$ requires N, 5·9%).

DL-threo-2-*Dichloroacetamido*-1-(3 : 4-*dichlorophenyl*)*propane*-1 : 3-*diol* (IV).—A mixture of the foregoing amine (1 g.) and methyl dichloroacetate (2 g.) was kept at 80° for 3 hours; the precipitate (1 g.) obtained on treatment with light petroleum crystallised from benzene in colourless leaflets, m. p. 91° (Found : C, 38·2; H, 3·5. $C_{11}H_{11}O_3NCl_4$ requires C, 38·0; H, 3·2%).

Note : It should be mentioned that the use of freshly distilled methyl dichloroacetate is indispensable in chloramphenicol studies, as this reagent rapidly becomes acid when kept, and then yields with amines mixtures of the required dichloroacetamides with amine dichloroacetates. This might perhaps account for the difficulties encountered by Long and Troutman (*J. Amer. Chem. Soc.*, 1950, **72**, 4299) in obtaining pure DL-*threo*-2-dichloroacetamido-1-*m*-nitrophenylpropane-1 : 3-diol.

Thanks are offered to La Société Belge de l'Axote (Liège) and to Dr. J. Guigan (Paris) for some microbiological asays, and to Miss P. F. Boshell, M.A. (Oxon), for assistance in this work.

DEPARTMENT OF ORGANIC CHEMISTRY,
RADIUM INSTITUTE, UNIVERSITY OF PARIS. [*Received, October 6th*, 1950.]

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60. *Triterpenoids. Part I. Morolic Acid, a New Triterpenoid Sapogenin.*

By D. H. R. BARTON and C. J. W. BROOKS.

The principal sapogenin from the heartwood of *Mora excelsa* Benth. has been shown to be a new triterpenoid hydroxy-acid, $C_{30}H_{48}O_3$, designated morolic acid. Replacement of the oxygen of this acid by hydrogen afforded the fundamental hydrocarbon identified as germanicene. Conversion of the carboxyl group into methyl gave germanicol. The action of acidic reagents on the oxide of methyl morolate acetate furnished, according to the proton-donating power of the medium, methyl olean-12 : 18-dienolate (methyl *iso*-dehydro-oleanolate) or methyl olean-11 : 13(18)-dienolate acetate (methyl dehydro-oleanolate acetate).

On melting, morolic acid decomposed to give oleanol in excellent yield, the same easy decarboxylation to the same product being observed with olean-13(18)-enolic acid.

Reduction of the above-mentioned oxide by lithium aluminium hydride followed by acetylation afforded a conjugated diene, shown to be norolean-16 : 18-dienyl acetate, the constitution of which was confirmed by a partial synthesis based on siaresinolic acid. This acetate was also obtained from the oxide of morolic acid acetate. It was smoothly isomerised by hydrogen chloride to norolean-12 : 18(17)-dienyl acetate, the constitution of which was proved by its formation from the facile decarboxylation of olean-12 : 18-dienolic acid.

These experiments provide evidence that morolic acid is olean-18-enolic acid.

The mechanism of the non-acid-catalysed decarboxylation of $\beta\gamma$-unsaturated acids is discussed. The theoretical correlation of the stabilisation of diolefinic systems with their degree of hyperconjugation is extended to include the conjugated dienes of the oleanolic acid series. Comment is made on the low intensity of absorption, in the ultra-violet region, of methyl olean-12 : 18-dienolate.

NATURALLY occurring saponins can be divided into two classes. The first of these gives steroidal sapogenins on hydrolysis, the second triterpenoid sapogenins. A consideration of molecular-rotation differences often helps in the assignment of a sapogenin to its correct class (Barton and Jones, *J.*, 1944, 659; Barton, *J.*, 1945, 813; 1946, 512, 1116; and later papers) and accordingly we welcomed the opportunity to investigate further a sapogenin obtained by

Farmer and Campbell (*Nature*, 1950, **165**, 237) at the Forest Products Research Laboratory, Princes Risborough, by acid hydrolysis of the saponin present in high concentration in the heartwood of *Mora excelsa* Benth. Our work on this problem was greatly facilitated by Mr. Campbell, who kindly provided us with an adequate supply of raw material, and by Sir John Simonsen, F.R.S., who gave us valuable advice in the initial stages of the investigation.

The first analyses of the crystalline sapogenin could be reconciled with the formula $C_{27}H_{42}O_3$ implying a steroid formulation. In apparent agreement acetylation afforded a monoacetate. However the specific rotation of the sapogenin ($[\alpha]_D$ +17° in acetone, +16° in dioxan, +13° in chloroform) rendered this somewhat questionable, since the steroid-sapogenin side chain normally confers pronounced lævorotation (Fieser and Fieser, " Natural Products Related to Phenanthrene," 3rd Edn., p. 591). Furthermore the change in molecular rotation on acetylation was +73°, which would correspond better with a triterpenoid than with a steroid formula (Barton, *loc. cit.*; the known steroidal sapogenins are all 3β-hydroxylated).

Further investigation of the sapogenin confirmed this view: it was shown to be a hydroxycarboxylic acid, $C_{30}H_{48}O_3$, by the preparation of a methyl ester, an acetate, an acetate methyl ester, and a benzoate methyl ester. The carboxyl group was sterically hindered and comparable in reactivity with that of oleanolic acid. The presence of 30 carbon atoms in the acid was shown by the equivalent of the acetate. The initial difficulty with regard to the analysis, referred to above, was due to solvation, the sapogenin crystallising well only from solvents containing methanol or another alcohol; analysis of a sample dried *in vacuo* at 160° was satisfactory for the unsolvated formula. The hydroxyl group was shown to be secondary by oxidation of the methyl ester by chromic acid to the corresponding ketone. Since this sapogenin is obtained from *Mora* wood and has one carboxyl and one hydroxyl group, we have named it morolic acid (Barton and Brooks, *J. Amer. Chem. Soc.*, 1950, **72**, 3314).

Although methyl morolate acetate resisted hydrogenation it gave a distinct colour with tetranitromethane indicative of unsaturation. Further, morolic acid, its acetate, methyl ester, methyl ester acetate, and methyl ester benzoate each absorbed one equivalent of oxygen from perbenzoic acid (see Table II, p. 269); the methyl ester acetate thus afforded the corresponding *oxide*, $C_{33}H_{52}O_4$, also obtained more expeditiously by the action of perhydrol–acetic acid at 100°. This oxide was saturated to tetranitromethane, thus indicating the presence of only one double bond in morolic acid. Triterpenoids of the β-amyrin series tend to furnish saturated ketones rather than epoxides under experimental conditions of this sort (*inter al.*, Ruzicka and Cohen, *Helv. Chim. Acta*, 1937, **20**, 804; Ruzicka, Müller, and Schellenberg, *ibid.*, 1939, **22**, 758; Picard, Sharples, and Spring, *J.*, 1939, 1045; Picard and Spring, *J.*, 1940, 1387). That the product from methyl morolate acetate was definitely an oxide was shown by its reaction with dry hydrogen chloride and with lithium aluminium hydride (see below).

Recently Ruzicka, Jeger, and their collaborators (*inter al.*, *Helv. Chim. Acta*, 1950, **33**, 672, 687, 711, 1050) have employed the presence or absence of an absorption maximum at about 11·8—12·4 μ. as indicative of a triply or fully substituted ethylenic linkage in triterpenoid compounds. Judged by this criterion the infra-red spectrum of methyl morolate acetate * (Fig. 1) indicated the presence of a triply substituted system $>C{=}CH-$.

At this stage of the investigation it was clear that morolic acid was a pentacyclic hydroxy-acid very probably belonging to the triterpenoid series. The next step was to convert the hydroxy-acid into the fundamental hydrocarbon. This was carried out by reduction of morolic acid, or better of its methyl ester, by an excess of lithium aluminium hydride, to moradiol, $C_{30}H_{50}O_2$, a new triterpenoid diol. Chromic acid oxidation followed by careful chromatography furnished the corresponding dicarbonyl derivative, moronal, characterised as the bis-2 : 4-dinitrophenylhydrazone. Wolff–Kishner reduction of moronal gave morene, which corresponded in m. p. to the hydrocarbon germanicene prepared recently by David (*Bull. Soc. chim.*, 1949, [v], **16**, 427) from germanicol. Subsequent work (see below) confirmed that the two hydrocarbons were identical.

Moradiol readily afforded a diacetate which, by partial alkaline hydrolysis, gave the secondary monoacetate, a reaction sequence paralleled by the behaviour of betulin. Moradiol monoacetate contains a primary hydroxyl group and afforded a toluene-*p*-sulphonate, reduction of which by lithium aluminium hydride furnished only moradiol (cf. Schmid and Karrer, *Helv. Chim. Acta*, 1949, **32**, 1371). Chromic acid oxidation of moradiol monoacetate followed by careful chromatography afforded the corresponding aldehyde, acetoxymoral, which on Wolff–

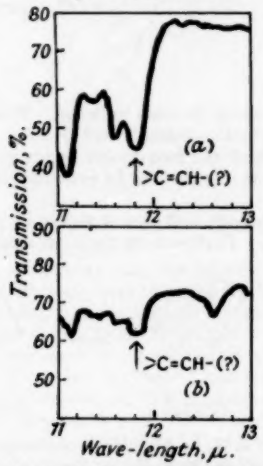
* We are indebted to Dr. R. Norman Jones of the N.R.C., Ottawa, for kindly making a preliminary determination of this spectrum. All the spectra reported here were taken at Harvard on the Baird Associates double-beam instrument (see Experimental).

Kishner reduction gave the alcohol, morol, $C_{30}H_{50}O$, together with some moradiol. Morol was shown to be identical with the known triterpenoid alcohol germanicol. This was established (see Experimental) by direct comparison with a specimen very kindly supplied by Dr. J. C. E. Simpson (*J.*, 1944, 283; cf. Dupont and Julia, *Bull. Soc. chim.*, 1947, [v], **14**, 1071) and confirmed by the identity of the infra-red spectra. A band near 12 μ. (see Fig. 2) confirms the trisubstituted nature of the ethylenic linkage.

The conversion of morolic acid into germanicol, which has been shown to belong to the β-amyrin–oleanolic acid group of triterpenoids (David, *ibid.*, 1949, [v], **16**, 155), establishes the triterpenoid nature of morolic acid and proves the position of the hydroxyl group, but it leaves undecided the precise location of the ethylenic linkage (see later) and the position of the carboxyl group. Evidence bearing on the latter problem was obtained by almost quantitative conversion of methyl morolate acetate oxide by hydrogen chloride into methyl dehydromorolate acetate, which was identical with methyl dehydro-oleanolate acetate obtained by selenium dioxide oxidation of methyl oleanolate acetate (Ruzicka, Grob, and van der Sluys-

FIG. 1.

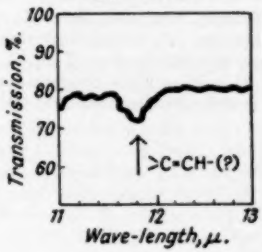
Methyl morolate acetate.



(*a*) *In* $CHCl_3$ (c, *approx.* 5·0).
(*b*) *In* CS_2 (c, *approx.* 5·0).

FIG. 2.

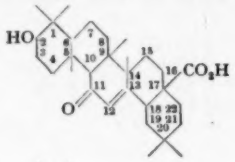
Morol, in $CHCl_3$ (c, *approx.* 5·0).

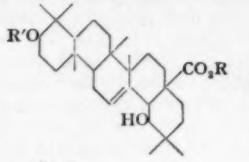


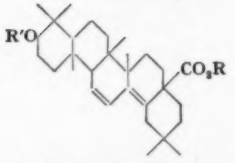
Veer, *Helv. Chim. Acta*, 1939, **22**, 788). This demonstrates that the carboxyl group of morolic acid is in the same position as in oleanolic acid.

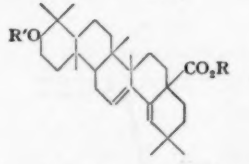
It is necessary at the present juncture to discuss the evidence bearing on the constitution of dehydro-oleanolic acid. This acid, or its simple functional derivatives, have been obtained in three ways. First, as the acetate methyl ester, by the route indicated above, secondly by the reduction of keto-oleanolic acid (I) by sodium and alcohol (Bilham, Kon, and Ross, *J.*, 1942, 532), and thirdly, as the acetate methyl ester, by the dehydration of methyl siaresinolate acetate (II; R = Me; R′ = Ac) by phosphoric oxide (Bilham, Kon, and Ross, *ibid.*, p. 540). Dehydro-oleanolic acid has two double bonds in conjugation in different rings as shown by the ultra-violet absorption maximum at 250 mμ. (Ruzicka, Grob, and van der Sluys-Veer, *loc. cit.*; cf. Ruzicka, Müller, and Schellenberg, *Helv. Chim. Acta*, 1939, **22**, 767) and, in view of the modes of formation mentioned above, two formulæ (III and IV; R = R′ = H) have been generally considered (compare the discussion by Green, Mower, Picard, and Spring, *J.*, 1944, 527). Ruzicka, Jeger, and Norymberski (*Helv. Chim. Acta*, 1942, **25**, 457) studied the oxidation of the analogous dehydro-β-amyrin acetate (V or VI) by lead tetra-acetate to give β-amyradienonyl acetate (VII) and considered that the formation of the latter provided firm evidence for the correctness of formula (VI). Actually this conclusion would be vitiated if, as is quite possible, the oxidation proceeded through the resonance-established radical (VIII)

and too much significance should not be attached to it. However, there are two other recorded facts with regard to the formation and reactions of dehydro-oleanolic acid which we believe to be of considerable diagnostic value. The first of these is the method of formation from (I). Double bonds in conjugation do *not* move under the influence of alkali to thermodynamically more stable positions unless they move into conjugation with other *unsaturated* substituents. The rearrangement of (III; R = R′ = H), the first product of the reduction of (I), to (IV;

(I.) 


(II.)

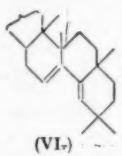
(III.) 

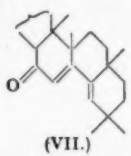

(IV.)

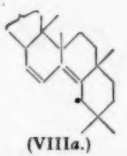
R = R′ = H) under the influence of alkali would, therefore, be very unlikely. This is strong evidence for formula (III). Secondly, the pyrolysis of dehydro-oleanolic acid affords "oleadienol I" (IX) (Bilham, Kon, and Ross, *J.*, **1942**, 532), in which the two double bonds have moved *out* of conjugation. As is discussed in greater detail below this can best be explained if dehydro-oleanolic acid is formulated as (III; R = R′ = H).

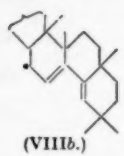
If (III; R = R′ = H) be the formula for dehydro-oleanolic acid then it should be possible to prepare an *iso*dehydro-oleanolic acid (IV; R = R′ = H). Furthermore the latter acid should be

(V.)

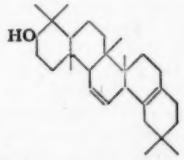

(VI.)

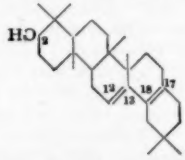

(VII.)


(VIII*a*.)


(VIII*b*.)

thermodynamically unstable with respect to (III; R = R′ = H), and should be rearranged thereto by acid in order to explain the observation by Bilham, Kon, and Ross (*loc. cit.*) on the dehydration of methyl siaresinolate acetate by phosphoric oxide. Both these predictions have been fulfilled. Oxidation of methyl morolate acetate by selenium dioxide afforded a methyl *iso*dehydro-oleanolate acetate which, unlike methyl dehydro-oleanate acetate ($[\alpha]_D$ −127°), exhibited pronounced dextro-rotation ($[\alpha]_D$ +209°). The corresponding methyl hydroxy-ester, obtained by fission of the oxide ring of methyl morolate acetate oxide, by heating with

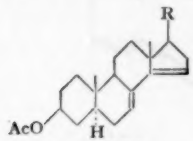
(IX.) 


(X.)

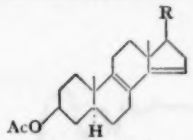
dilute methanolic sulphuric acid, also showed a pronounced dextrorotation ($[\alpha]_D$ +214°) and exhibited a maximum at 237 mμ. indicative of the presence of two double bonds in different rings. Isomerisation of methyl *iso*dehydro-oleanolate acetate by hydrogen chloride gave methyl dehydro-oleanolate acetate (III; R = Me, R′ = Ac) in almost quantitative yield. That *iso*dehydro-oleanolic acid, prepared by vigorous alkaline hydrolysis of the acetate methyl ester, possesses the formula (IV; R = R′ = H) was confirmed by pyrolysis, which furnished in good yield a nor-dienol, $C_{29}H_{46}O$, m. p. 189—191°, $[\alpha]_D$ +79°, in which the two double

bonds had *remained* in conjugation as shown by the ultra-violet absorption spectrum of the derived acetate ($\lambda_{max.}$ 238 and 244 mμ.; ε = 16,700, and 18,800 respectively). We formulate this dienol as (X) [norolean-12 : 18(17)-dienol],* the mechanism of its genesis being discussed in greater detail below.

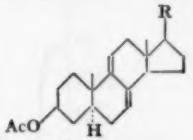
The correctness of the formulæ (III; R = R′ = H) and (IV; R = R′ = H) for dehydro- and *iso*dehydro-oleanolic acids is further confirmed by their absorption spectra. It has been enunciated as a general principle that cisoid chromophores absorb with lower intensity than the corresponding transoid chromophores (*inter al.*, Koch, *Chem. and Ind.*, 1942, **61**, 273; Braude *et al.*, *J.*, 1949, 1890, and references there cited). In agreement with this we have found that ergosterol B_3 acetate (XI; R = C_9H_{17}) (cf. Barton, *J.*, 1946, 512; for an improved method of preparation see Experimental) has a low-intensity absorption band ($\lambda_{max.}$ 242 mμ.; ε = 9900) relative to dehydro-α-ergostenyl acetate (XII; R = C_9H_{17}) ($\lambda_{max.}$ 248 mμ.; ε = 19,800) and ergosteryl D acetate (XIII; R = C_9H_{17}) ($\lambda_{max.}$ 242 mμ.; ε = 13,200) (see Barton and Cox, *J.*, 1949, 219). In the first-named of these acetates the chromophore is cisoid, in the other two it is transoid. Compounds of the β-amyrin series with two double bonds as in dehydro-



(XI.)



(XII.)



(XIII.)

oleanolic acid (III; R = R′ = H) absorb at 250 mμ. with ε about 25,000 (*inter al.*, Ruzicka, Grob, and van der Sluys-Veer, *Helv. Chim. Acta*, 1939, **22**, 788; Ruzicka, Müller, and Schellenberg, *ibid.*, p. 767), the high intensity of absorption corresponding to a transoid chromophore. In *iso*dehydro-oleanolic acid the value of ε is only about 10,000 (see Experimental) as expected for a cisoid chromophore.

It was of interest that the physical constants found by us for norolean-12 : 18(17)-dienol were quite close to those recorded by Noller and Carson (*J. Amer. Chem. Soc.*, 1941, **63**, 2238) and by Bilham, Kon, and Ross (*J.*, 1942, 535) for norechinocystadienol. Through the courtesy of Professor C. R. Noller (Stanford University, California) who kindly supplied us with an authentic specimen of norechinocystadienol, we have been able to compare the two alcohols directly. As shown in Table I and discussed at greater length in the Experimental section there can be little doubt that norechinocystadienol is substantially norolean-12 : 18(17)-dienol. This is in agreement with Noller and Carson's proposed formula (*loc. cit.*). The infra-red absorption spectra (Figs. 3 and 4) of the two alcohols were identical except for a small difference in relative intensity in two bands in the 9·6—10·2-μ. region.

* The nomenclature used in this paper is as follows. The syllable " olean " is considered a trivial designation for the C_{30} carbon skeleton [as in (I)] having the steric orientation present in β-amyrin and oleanolic acid. The fully saturated C_{30} hydrocarbon derived from oleanolic acid formally by reduction and the changes $CO_2H \longrightarrow CH_3$ and $OH \longrightarrow H$ is termed oleanane, and the derived unsaturated hydrocarbons are termed oleanene, oleandiene, etc. The derived C_{30} alcohols and ketones are named by the usual variations of the termination. Acids derived from the hydrocarbons by oxidation of a methyl group to carboxyl are termed oleananoic, oleandienoic acid, etc. (names of the type oleanane-carboxylic acid, which have been used, are incorrect as the addition of the carboxylic acid suffix indicates a C_{31} structure). When a hydroxyl group is present in such acids, the name ends in " olic acid," as in oleanenolic acid, oleandienolic acid, thus preserving the termination current for triterpenoid sapogenin acids. When a methyl group is replaced by hydrogen, giving a C_{29} compound, the prefix " nor " is used; this gives, *e.g.*, the name noroleandienol for (X); it will be noted that this replacement of methyl by hydrogen in the hydrocarbon is, in some cases, equivalent to decarboxylation of the corresponding acid. Numerals are used, as usual, for designation of the position of unsaturation or groups; such numerals need not normally be used for the hydroxyl or the carboxyl group of hydroxy-acids whose names end in " olic acid," the syllables " olean " being held to denote specifically that the hydroxyl and the carboxyl group are present at position 2 and 17 respectively. The term " oleanolic acid " is regarded as wholly trivial (as are its dehydro- and other derivatives), being equivalent to olean-12-enolic acid. It is hoped that this system may prove of general applicability in the triterpene field in cases when a " parent " name has been agreed. It is in agreement with the system of nomenclature adopted by the Swiss School, except for minor points. It may be noted that the name " oleanane " does not itself define the stereochemical orientation at $C_{(18)}$ or, yet, at $C_{(18)}$; the " olean " prefix, which defines the stereochemistry, is derived from oleanolic acid which is unsaturated at positions 12 : 13; and the orientation of the hydrogen atom at position 18 is uncertain (cf. XIV and XV); these problems will be considered in a forthcoming paper. [D. H. R. B. and the Editor.]

As would be expected, the reactions described above for morolic acid and its derivatives are paralleled in a number of cases by those recorded recently by David (*Bull. Soc. chim.*, 1949 [v], **16**, 155, 427; 1950, [v], **17**, 169) for germanicol and its derivatives. Although David tentatively accepted the incorrect formula for dienes of the dehydro-oleanolic acid type, his

TABLE I.

	Alcohol,		Acetate,		Benzoate,	
Substance.	m. p.	$[\alpha]_D$.	m. p.	$[\alpha]_D$.	m. p.	$[\alpha]_D$.
Norolean-12 : 18(17)-dienol	189—191°	+79°	187—188°	+66°	227—229°	+80°
Norechinocystadienol	189—191	+82 *	186—188	+46 †	231—233 *	—

* In dioxan; Noller and Carson, *J. Amer. Chem. Soc.*, 1941, **63**, 2238.
† In dioxan; Bilham, Kon, and Ross, *J.*, 1942, 535.

FIG. 3.

Olean-12 : 18(17)-*dienol in* $CHCl_3$ (c, *approx.* 2·0).

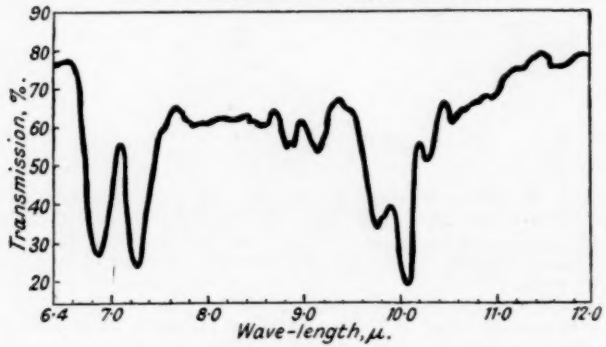
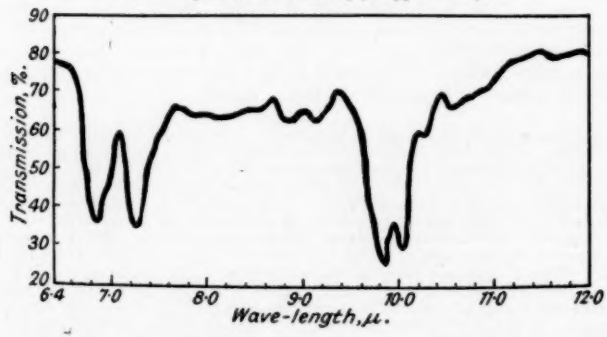


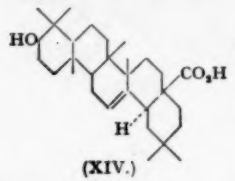
FIG. 4.

Norechinocystadienol in $CHCl_3$ (c, *approx.* 2·0).

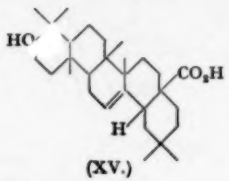


conclusion that the double bond in germanicol must be at one of the positions 12(13), 13(18), or 18(19) seems to us reasonable. There are then five possible formulæ (XIV—XVIII) for morolic acid. One of these (XIV or XV) must be the formula of oleanolic acid. The formula (XVI) has been proposed by Jeger, Norymberski, and Ruzicka (*Helv. Chim. Acta*, 1944, **27**, 1532; compare the corresponding β-amyrin analogue described by Ruzicka and Jeger, *ibid.*, 1941, **24**, 1236) for the acid from the hydrogenation product (methyl δ-oleanolate acetate) of methyl dehydro-oleanolate acetate (III; R = Me; R′ = Ac), on the grounds that it affords an oxide stable in hot acetic acid, conditions under which 12(13)-epoxides of the β-amyrin series are rearranged to the corresponding saturated ketones (cf. Ruzicka and Cohen, *ibid.*, 1937, **20**, 804; Ruzicka, Müller, and Schellenberg, *ibid.*, 1939, **22**, 758; Picard, Sharples, and

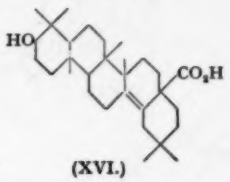
Spring, *J.*, 1939, 1045; Picard and Spring, *J.*, 1940, 1387, and later papers). Although we do not regard this evidence as particularly relevant a study of the reactions of the corresponding acid (δ-oleanolic acid) has confirmed this formula (see below). Methyl olean-13(18)-enolate acetate was also obtained (see Experimental) by the similar hydrogenation of methyl *iso*-dehydro-oleanolate acetate (IV; R = Me, R′ = Ac). The latter method of formation is a good example of 1 : 4-addition in catalytic hydrogenations (cf. Barton and Cox, *J.*, 1949, 214).



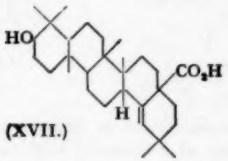
(XIV.)



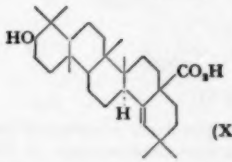
(XV.)



(XVI.)



(XVII.)



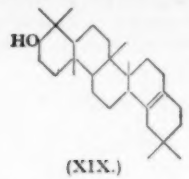
(XVIII.)

Attempts to characterise the double bond in morolic acid by the standard methods of oxidative attack proved fruitless. Methyl morolate acetate was completely resistant to osmium tetroxide. Ozonolysis afforded either unchanged starting material or, in quite good yield, the oxide. Chromic acid oxidation followed by careful chromatography furnished, besides unchanged starting material, the O_7 compound, $C_{32}H_{44}O_7$, previously obtained by Mower, Green, and Spring (*J.*, 1944, 256) by chromic acid oxidation of methyl dehydro-oleanolate acetate. Since the constitution of this compound is still unknown (see Jeger, Norymberski, and Ruzicka, *Helv. Chim. Acta*, 1944, **27**, 1532) its formation provides no evidence as to the position of the double bond in morolic acid.

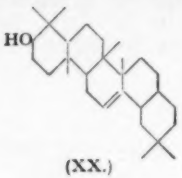
The first evidence bearing on the position of this double bond comes from the failure of morolic acid to lactonise under conditions adequate for the lactonisation of oleanolic acid. The carboxyl group in oleanolic acid must be polar in the stereochemical sense (for a discussion see Barton, *Experientia*, 1950, **6**, 316) in order to explain lactonisation. Inversion at $C_{(18)}$ should not alter this relationship and therefore 18-*iso*oleanolic acid should lactonise as readily as oleanolic acid.

By elimination then, formula (XVII) or (XVIII) is indicated for morolic acid, the double bond being in the βγ-position to the carboxyl group. It is a general rule that βγ-unsaturated acids are decarboxylated with ease on pyrolysis (for example, Arnold, Elmer, and Dodson, *J. Amer. Chem. Soc.*, 1950, **72**, 4359) and, as originally shown by Wallach (*Annalen*, 1906, **347**, 316; 1907, **353**, 287; 1908, **359**, 291; 1908, **360**, 26), the elimination of carbon dioxide is always accompanied by a shift of the double bond to the αβ-position. It is also true that many αβ-unsaturated acids are readily decarboxylated but, at least in the case of tertiary βγ-unsaturated acids, a shift of the double bond to the αβ-position *cannot* precede decarboxylation. It was therefore an important observation in the chemistry of morolic acid when it was discovered that the acid was very easily decarboxylated, merely on melting, to give an almost quantitative yield of oleanol. Oleanol had previously been prepared by Winterstein and Stein (*Z. physiol. Chem.*, 1931, **202**, 222) by pyrolysis of oleanolic acid. It is important that this latter preparation proceeds slowly, at nearly 100° above the decomposition (melting) temperature of morolic acid, in half an hour as opposed to the time taken in melting the morolic acid (a few seconds) and gives a poor yield of an impure product. In our opinion this remarkable contrast in reaction rate is best explained if morolic acid is βγ-unsaturated and oleanolic acid γδ-unsaturated. Oleanol then must have the formula (XIX) and not that (XX) previously accepted for this alcohol (see Elsevier's " Encyclopædia of Organic Chemistry," Vol. XIV, p. 544). In agreement, the infra-red spectrum of oleanol (Fig. 5) showed no significant absorption maximum in the region 11·8—12·4 μ., thus indicating a fully substituted and not a trisubstituted ethylenic linkage. As to the mechanism whereby oleanol is obtained from oleanolic acid, it is possible

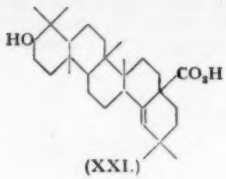
that the reaction proceeds by lactonisation, followed by isomerisation to olean-13(18)-enolic acid which, being βγ-unsaturated, would be decarboxylated easily. In agreement with this view pyrolysis of oleanolic lactone gave, in poor yield, oleanol.



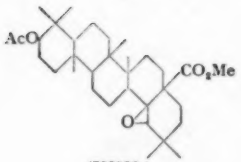
(XIX.)



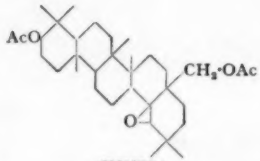
(XX.)



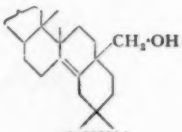
(XXI.)



(XXII.)



(XXIII.)

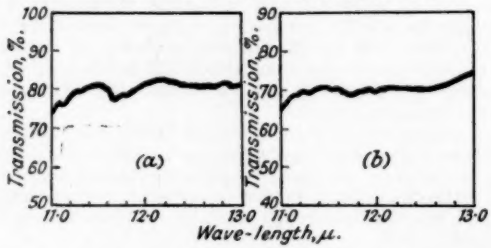


(XXIV.)

The above pyrolysis evidence is indicative of βγ-unsaturation in morolic acid. In order to exclude further consideration of (XVI) a brief study of δ-oleanolic acid was undertaken. Since this acid (as the methyl ester acetate) is obtained by the hydrogenation of (III; R = Me,

FIG. 5.

Oleanol, (a) in $CHCl_3$, *(b) in* CS_2 (c, *approx.* 5·0).

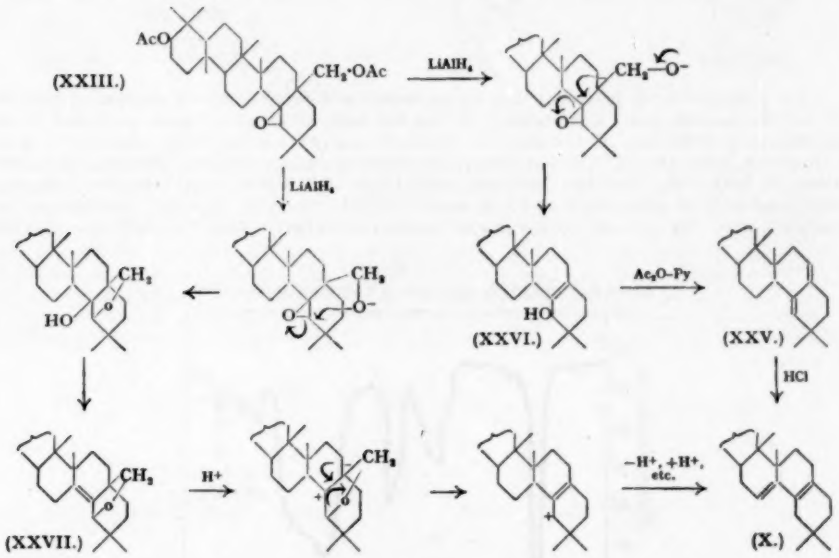


R′ = Ac) the ethylenic linkage must be at position 12(13) or 13(18) and not at 18(19).* δ-Oleanolic acid, prepared by vigorous alkaline hydrolysis of the methyl ester acetate, showed no tendency to give a bromo-lactone under conditions adequate for the formation of this derivative from oleanolic acid. It melted with vigorous decomposition (252—254°) and thereby afforded oleanol with the same ease as did morolic acid. Its formulation as the βγ-unsaturated olean-13(18)-enolic acid is thus confirmed. By exclusion then, morolic acid must be olean-18-enolic acid (XXI), and the methyl ester acetate oxide must be (XXII).

Further evidence as to the βγ-unsaturation of morolic acid was obtained in the following way. It was expected that lithium aluminium hydride reduction of moradiol diacetate oxide (XXIII) might open the oxide ring and give a triol or its dehydration product, for example (XXIV). In fact the reduction product, after acetylation and careful chromatography, furnished two compounds. The major product was an unsaturated acetate, $C_{31}H_{48}O_2$, m. p. 220—222°, $[\alpha]_D$ −19°. The preparation of (XXIV) by lithium aluminium hydride reduction of methyl olean-13(18)-enolate acetate proceeded without difficulty and the derived diacetate was quite different from the oxide reduction product. Hydrolysis of the acetate of m. p. 220—222° gave the corresponding alcohol, $C_{29}H_{46}O$, m. p. 181—183°, $[\alpha]_D$ −45°. A rational interpretation of these compounds became possible when it was discovered that they were

* Double bonds at positions 12(13), 13(18), and 18(19) in the triterpenoid skeleton, unlike those at 7(8) and 8(9) in the steroid series, show no indication of rearrangement under standard hydrogenating conditions (Pt–H_2 and acetic acid). Therefore this evidence is probably of diagnostic significance.

unsaturated conjugated dienes ($\lambda_{max.}$ 241 mμ.; ε = 17,200) with the double bonds in different rings. We formulate the dienol acetate as norolean-16 : 18-dienyl acetate (XXV) and interpret its formation by the mechanism outlined in the scheme. This mechanism implies that an intermediate allylic alcohol (XXVI) is formed, and this was proved to be the case although the intermediate was unstable and was not characterised. The second product of



the reduction was obtained as the acetate, $C_{32}H_{50}O_3$, m.p. 248—250°, $[\alpha]_D$ −2°, which was unsaturated to tetranitromethane, gave no hydroxyl band in the infra-red spectrum (confirmed by the ready elution from alumina), and showed the ordinary acetate carbonyl band at 5·75 μ. In view of the mode of preparation a ketonic carbonyl group can hardly be present. The infra-red spectrum (Fig. 6) showed a small absorption band near 9 μ. Such bands as this have been interpreted (Ruzicka, Baumgartner, and Prelog, *Helv. Chim. Acta*, 1949, **32**, 2069; Meyer, Jeger, and Ruzicka, *ibid.*, 1950, **33**, 687) as indicative of ethereal oxygen.* If this assignment is correct then a possible formula for the by-product would be (XXVII), its formation proceeding as indicated.

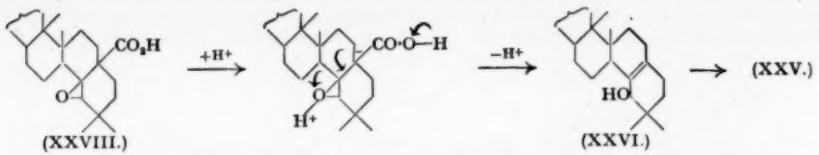
On treatment with dry hydrogen chloride norolean-16 : 18-dienol acetate furnished, in excellent yield, norolean-12 : 18(17)-dienol acetate (as X). The same acetate was obtained in the same way from the by-product acetate (? XXVII). Whilst the first-mentioned rearrangement is easily explained in terms of the addition and abstraction of protons, it is rather more difficult to rationalise the second. One possibility is indicated in the scheme above.

Reduction of methyl morolate acetate oxide by lithium aluminium hydride followed by acetylation also afforded norolean-16 : 18-dienol acetate, but there was no indication of the formation of the by-product acetate. It is very difficult to explain these remarkable elimination reactions other than on the basis of a βγ-oxido-structure for the starting material.

A further indication of the βγ-unsaturation of morolic acid was furnished by examination of the action of perbenzoic acid on morolic acid acetate. As mentioned above (p. 258) this compound consumes one equivalent of oxidant only. However, working up the product in the usual way afforded both an acid and a neutral fraction. We defer our report on the nature of the former fraction, but the neutral fraction was identified as pure norolean-16 : 18-dienol

* It is our experience that substances containing ethereal oxygen do exhibit a band at about 9 μ., but, on the other hand, so do many compounds in the steroid field lacking this function. It is, therefore, necessary to interpret evidence of this type with caution.

acetate. Presumably the βγ-oxido-acid acetate (XXVIII) is unstable under the mild acid conditions used in working up and decomposes as indicated below.

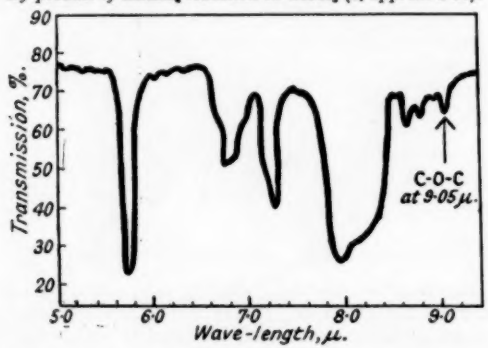


(XXVIII.) (XXVI.)

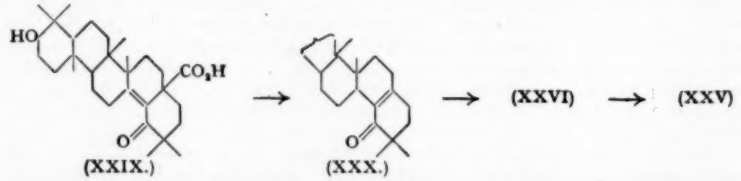
The evidence so far presented may be construed as a proof of the correctness of formula (XXI) for morolic acid. Confirmation of this has been obtained by what we regard as an unambiguous synthesis of norolean-16 : 18-dienol acetate starting from siaresinolic acid. Siaresinolic acid (II; R = R′ = H) was converted by known methods (Bilham, Kon, and Ross, *J.*, 1942, 540; Ruzicka, Grob, Egli, and Jeger, *Helv. Chim. Acta*, 1943, **26**, 1218) into 2-hydroxy-19-keto-olean-13(18)-en-17-oic acid (XXIX), pyrolysis of which furnished, after acetylation of the product and chromatography, 2-acetoxynorolean-17-en-19-one (XXX).

FIG. 6.

By-product of $LiAlH_4$ *reduction in* $CHCl_3$ (c, *approx.* 1·00).

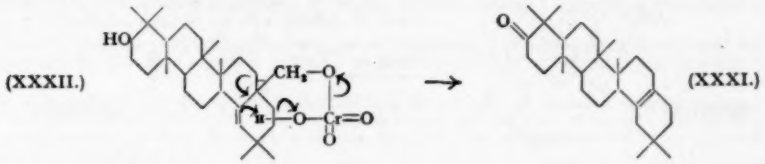


The position of the double bond in this compound is based on the general rule of βγ ⟶ αβ shift in the decarboxylation of βγ-unsaturated acids (see above) and is confirmed by the large change in rotation {the methyl ester of (XXIX) has $[\alpha]_D$ −209°; the acetate (XXX) shows $[\alpha]_D$ +138°}. The product was further characterised by hydrolysis to 2-hydroxynorolean-17-en-19-one. Reduction of 2-acetoxynorolean-17-en-19-one by lithium aluminium hydride gave an unstable compound of indefinite properties [presumably (XXVI)] which, on acetylation, furnished authentic norolean-16 : 18-dienol acetate, identical with the acetate obtained earlier from morolic acid.

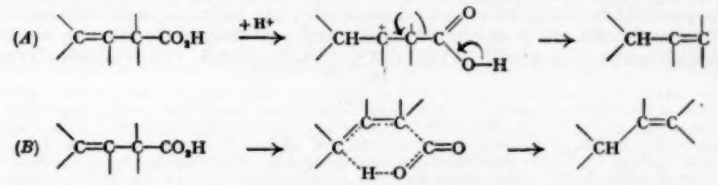


The behaviour of moradiol and of moradiol monoacetate on chromic acid oxidation, some aspects of which have already been discussed above, is deserving of further mention. The reaction products in both cases proved unexpectedly complex (for details see Experimental). Chromatography of the moradiol oxidation product afforded, in the most easily eluted fraction, oleanone (XXXI). The most easily eluted fraction of the monoacetate oxidation product

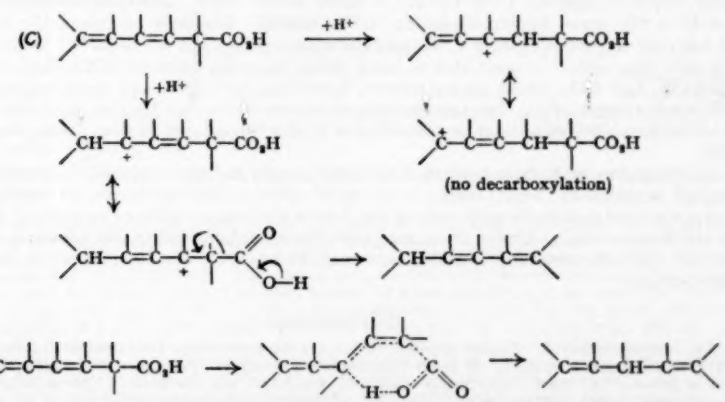
was likewise indicated to be the acetate of oleanol (XIX). Under the same conditions morolic acid acetate was recovered unchanged. These interesting by-products may be formed from the corresponding aldehydes, or possibly by an intramolecular process within a chromic acid ester as *illustrated* only in (XXXII). In any case we regard these reactions as additional evidence for $\beta\gamma$-unsaturation in morolic acid.



The evidence which has been accumulated on the constitution of morolic acid also enables one point of stereochemistry to be elucidated. There are two possible formulæ for morolic acid, (XVII) and (XVIII). In our opinion the evidence shows that the former of these is correct. There are two (more probable) general mechanisms which will explain the shift of the double bond from the $\beta\gamma$- to the $\alpha\beta$-position during decarboxylation of acids of the morolic acid type. In the first of these (*A*) a β-carbonium ion is formed, in the second (*B*) the transition state is of the intramolecular type without separation of charge (for example see Johnson and Hunt, *J. Amer. Chem. Soc.*, **1950**, **72**, **935**; we are indebted to Professor W. S. Johnson, University of Wisconsin, for an interesting discussion). Mechanism (*A*) should proceed best in the presence

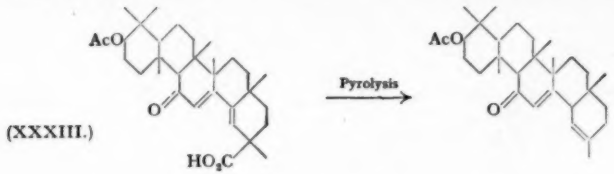


of acids, mechanism (*B*) should be the preferred one in the gaseous phase. It should be possible to distinguish between these two mechanisms by studying the decomposition of $\beta\gamma$: $\delta\epsilon$-dienoic acids, for according to mechanism (*A*), as in (*C*), the two double bonds in the decarboxylated product should remain in conjugation, whereas according to mechanism (*B*), as in (*D*), they should shift out of conjugation.



Two examples are recorded in the triterpenoid field whereby to test this theory. The first has been mentioned in the discussion of the constitution of dehydro-oleanolic acid (see above).

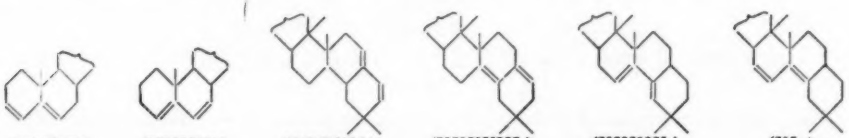
The second is the pyrolysis of dehydroglycyrrhetic acid acetate (XXXIII) at 205—210° to give nor-β-amyradienonyl acetate (XXXIV) (Ruzicka and Jeger, *Helv. Chim. Acta*, 1942, **25**, 775). In both cases the double bonds move out of conjugation; therefore the reactions must proceed by mechanism (*B*).



(XXXIII.) (XXXIV.)

Now norolean-16 : 18-dienol acetate has been obtained by two routes. That from morolic acid does not involve $C_{(13)}$; the other proceeds from siaresinolic acid and includes a decarboxylation. Siaresinolic acid has the $C_{(17)}$-carboxyl group in the same configuration as in oleanolic acid and it must be polar in the stereochemical sense in order to explain the ease of lactonisation on to $C_{(13)}$. In the decarboxylation of (XXIX) the C–H bond formed at $C_{(13)}$ must be on the *same* side of the molecule as the original C–carboxyl bond. The configuration at $C_{(13)}$ must be the same in morolic acid and therefore the formula (XVII) is correct.

A further point of theoretical interest in connection with these researches concerns the thermodynamic stability of olefinic or dienic systems. De La Mare, Hughes, and Ingold (*J.*, 1948, 17) have pointed out that in a number of aliphatic systems the stability of ethylenic linkages is governed by the number of C–H bonds that can hyperconjugate therewith. This is a useful generalisation which can be extended, albeit with caution for there are exceptions, to conjugated dienes in the steroid and di- and tri-terpenoid fields. Thus cholesta-3 : 5-diene



(XXXV.) (XXXVI.) (XXXVII.) (XXXVIII.) (XXXIX.) (XL.)

(XXXV) is more stable than cholesta-4 : 6-diene (XXXVI). The former has four hyperconjugating C–H bonds, the latter only three. Dehydro-oleanolic acid (III; R = R′ = H) (three hyperconjugating C–H bonds) is more stable than *iso*dehydro-oleanolic acid (IV; R = R′ = H) (two hyperconjugating C–H bonds). Similarly norolean-12 : 18(17)-dienol (X) with six hyperconjugating C–H bonds is more stable than norolean-16 : 18-dienol (XXV) with only two such. It must also be more stable than the alcohols (XXXVII), (XXXVIII), (XXXIX), and (XL) which, in agreement, have two, four, two, and three hyperconjugating C–H bonds respectively. The most serious exception to the rule that we have encountered so far is the instability of neoabietic acid relative to abietic acid (see Barton, *Quart. Reviews*, 1949, **3**, 36).

In connection with these aspects of thermodynamic stability it should be emphasised that, although norolean-12 : 18(17)-dienol is the most stable of the nor-dienes, its formation in the pyrolysis of *iso*dehydro-oleanolic acid is not due to the isomerisation of an initially formed and less stable nor-dienol. Under the same pyrolytic conditions and in the presence of oleanolic acid the thermodynamically unstable norolean-16 : 18-dienol acetate showed no indication of isomerisation.

Experimental.

M.p.s are uncorrected. Unless specified to the contrary rotations were determined for the sodium D line, in chloroform solution, at room temperature (15—25°). For polarimetry all specimens were dried *in vacuo* at 20° below their m. p.s or at 110°, whichever was the lower. Values of $[\alpha]_D$ have been approximated to the nearest degree. For the calculation of molecular rotations, $[\alpha]$ at *c*, 2·00, or at the nearest concentration to this at which measurements were made, have been used.

Unless specified to the contrary, infra-red spectra were determined in chloroform solution, with a Baird Associates (Cambridge, Mass., U.S.A.) self-recording double-beam instrument.

We are indebted to Dr. E. A. Braude (Imperial College) and Mr. Huang (Harvard) for determination of ultra-violet absorption spectra; solutions in absolute alcohol were used.

Merck's alumina for chromatography was used unless specified to the contrary.

In the text below the phrase " in the usual way " refers to dilution with water, extraction with ether, washing successively with aqueous potassium hydroxide, aqueous hydrochloric acid, and water, followed by evaporation of the ethereal solution *in vacuo*. Where necessary, water was removed from the residue by azeotropic distillation with benzene *in vacuo*.

Alkaline hydrolyses were effected by using several equivalents of potassium hydroxide and refluxing the reactants for 30—60 minutes in methanol or dioxan–methanol according to the solubility of the ester.

For methylations with diazomethane the acid was treated with an excess of ethereal diazomethane. After the mixture had been kept at room temperature until the evolution of nitrogen had ceased (about 30 minutes for 2-g. portions of morolic acid) the excess of diazomethane and the ether were removed *in vacuo* or on the steam-bath.

Morolic Acid from Mora *Saponin*.—The following procedure was found to be satisfactory. The saponin was heated under reflux (oil-bath) with alcohol (10 ml. per g. of saponin) containing concentrated hydrochloric acid (2 ml. per g. of saponin). The saponin first formed a deep-red solution which, after refluxing for a short time, began to deposit a crystalline precipitate of sapogenins. After 2 hours' refluxing, the mixture, now thick from the crystalline sapogenins, was allowed to cool and the precipitate was filtered off and washed with methanol. The crude sapogenin mixture was recrystallised several times from dioxan–methanol. 480 G. of saponin furnished 35 g. of pure *morolic acid*, m. p. 273° (decomp.), $[\alpha]_D$ +16° (*c*, 1·80 in dioxan), +33° (*c*, 0·59), +31° (*c*, 0·71) (Found: C, 76·5; H, 10·7. $C_{30}H_{48}O_3,CH_3{\cdot}OH$ requires C, 76·2; H, 10·7%). This represents a yield of 7·3%, as against 9·4% found by the Forest Products Research Laboratory (see Table III below) for material of somewhat lower m. p. The yield of acid of m. p. 263° was 42 g. (8·8%) and thus the results are in good agreement. Morolic acid was sparingly soluble in ethyl acetate or chloroform and tended to separate in an amorphous state unless methanol (or another alcohol) was present. Morolic acid showed no absorption in the ultra-violet region above 220 mμ. The acid was recovered unchanged after treatment adequate for the formation of a lactone (Winterstein and Stein, *Z. physiol. Chem.*, 1931, **199**, 64) or bromo-lactone (Winterstein and Stein, *ibid.*, pp. 50, 64) from oleanolic acid. On titration with perbenzoic acid in chloroform solution morolic acid consumed one equivalent of oxidant only (see Table II below).

Morolic Acid Acetate.—Morolic acid was refluxed with acetic anhydride for 1 hour. Working up in the usual way afforded the *acetate* which, recrystallised from chloroform–methanol or ethyl acetate–methanol, had m. p. 256—257° (decomp.), $[\alpha]_D$ +42° (*c*, 2·31), +44° (*c*, 1·77) (for analysis see Table III below). The equivalent weight of morolic acid acetate was determined by titration (phenolphthalein) with a solution of potassium hydroxide in dioxan–methanol, oleanolic acid having been used for standardisation (Found: equiv., 498. $C_{32}H_{50}O_4$ requires equiv., 499). The acetate gave a very pale yellow colour with tetranitromethane. For the titration with perbenzoic acid see Table II.

Methyl Morolate.—Morolic acid was esterified with diazomethane in the usual way. Recrystallised from ethyl acetate–methanol, the *methyl* ester had m. p. 228—229°, $[\alpha]_D$ +26° (*c*, 3·27), +26° (*c*, 2·21) +26° (*c*, 1·73) (Found: C, 78·7; H, 10·4. $C_{31}H_{50}O_3$ requires C, 79·1; H, 10·7%). 30 Mg. of the ester, refluxed with 200 mg. of potassium hydroxide in 10 ml. of methanol for half an hour and then left for 3 days, was almost quantitatively recovered unchanged. For the titration with perbenzoic acid see Table II.

TABLE II.

*Perbenzoic acid titrations.**

Substance.	Equivs. of per-acid consumed.	Substance.	Equivs. of per-acid consumed.
Morolic acid	0·91	Morolic acid acetate methyl ester	0·89, 1·10
Morolic acid acetate	0·97	Morolic acid benzoate methyl ester	1·00
Morolic acid methyl ester	0·89		

* In chloroform solution. The course of the reaction was followed until the uptake of per-acid was complete.

Methyl Morolate Acetate.—The methyl ester was refluxed with acetic anhydride for 30 minutes. Working up in the usual way and crystallisation of the product from chloroform–methanol afforded *methyl morolate acetate*, m. p. 263—264°, $[\alpha]_D$ +37° (*c*, 1·82), +38° (*c*, 1·76) (Found: C, 77·0; H, 10·05. $C_{33}H_{52}O_4$ requires C, 77·3; H, 10·2%). This gave a yellow colour with tetranitromethane, but resisted hydrogenation over a platinum catalyst in ethyl acetate at room temperature, in acetic acid at room temperature, or in acetic acid at 50°. In the Liebermann–Burchard reaction the initial colour was pink-blue, deepening to a permanent violet. This ester acetate was not isomerised when 100 mg. were heated in 10 ml. of acetic acid, to which two drops of concentrated sulphuric acid had been added, for 3 hours on the steam-bath. It was completely resistant to osmium tetroxide in ether (6 days at room temperature) and in dry pyridine (8 weeks at room temperature, then 8 hours at 100°); the starting material was recovered almost quantitatively in both cases. For the titration with perbenzoic acid see Table II.

In comparative experiments, methyl oleanolate acetate and olean-13(18)-enolate acetate were each recovered (almost quantitatively) unchanged after similar treatment with osmium tetroxide in dry pyridine.

Methyl Morolate Benzoate.—The methyl ester was heated in pyridine solution for 1½ hours at 100° with an excess of benzoyl chloride. Working up in the usual way afforded the *benzoate*, m. p. 194—195° (from ethyl acetate–methanol), $[\alpha]_D$ +52° (*c*, 2·08) (Found: C, 78·7; H, 9·2. $C_{38}H_{54}O_4$ requires C, 79·4; H, 9·45%). For the titration with perbenzoic acid see Table II.

Methyl Moronate.—Methyl morolate (0·5 g.) in ether–acetic acid was oxidised by chromic acid (excess) overnight. Working up in the usual way gave *methyl moronate* (400 mg.) which, recrystallised from methanol, had m. p. 165°, $[\alpha]_D$ +59° (*c*, 4·71), +58° (*c*, 4·59) (Found: C, 79·65; H, 10·2. $C_{31}H_{48}O_3$ requires C, 79·45; H, 10·3%).

Examination of Total Sapogenin Fraction.—By hydrolysis of *Mora* saponin with alcoholic hydrochloric acid the Forest Products Research Laboratory (F.P.R.L.), had obtained the total sapogenin fraction and had divided this into four main sub-fractions, hereinafter referred to as sapogenins I, II, III, and IV. The data * on these sapogenins, collected by the F.P.R.L., are summarised in Table III.

TABLE III.

Sapogenin fractions from Mora excelsa *Benth.*

Sapogenin.*	I.	II.	III.	IV.
Yield (on wt. of saponin), %	9·4	3·9	3·5	1·0
M. p.	261—263°	267—274°	241—245°	283—286°
$[\alpha]_D$ (in $CHCl_3$)	+30° +17° (in $COMe_2$)	+62°	+64°	+79°
Found (%)	C, 76·7; H, 10·6	C, 77·8; H, 10·6	C, 77·7; H, 10·35	C, 78·75; H, 10·6
$C_{30}H_{48}O_3.C_2H_5{\cdot}OH$ requires (%)	C, 76·45; H, 10·8	—	—	—
Calc. for $C_{30}H_{48}O_3$ (%)	—	—	—	C, 78·9; H, 10·6
Loss in wt. at 160° *in vac.* (2 hrs.) (%)	4·2	0·5	0·0	—
Found (after heating as above) (%)	C, 78·5; H, 10·5	C, 78·55; H, 10·5	C, 77·8; H, 10·3	—
Acetate, m. p.	245—247°	252—254·5°	—	256—258°
Found (%)	C, 76·9; H, 10·15	C, 77·10; H, 10·1	—	—
$C_{32}H_{50}O_4$ requires (%)	C, 77·05; H, 10·1	C, 77·05; H, 10·1	—	—

* Arranged in order of increasing solubility in alcohol. Sapogenin IV was only deposited on prolonged storage of the filtered hydrolysate.

The least soluble fraction, sapogenin I, consisted of morolic acid.

Sapogenin IV was methylated with diazomethane and then acetylated; one recrystallisation from chloroform–methanol furnished methyl oleanolate acetate, m. p. 218°, $[\alpha]_D$ +69° (*c*, 4·09), which gave no depression in m. p. on admixture with an authentic specimen of m. p. 218°, $[\alpha]_D$ +69° (*c*, 1·99), obtained from oleanolic acid extracted from spent cloves.† Alkaline hydrolysis of the acetate ester of sapogenin IV afforded the corresponding methyl ester, m. p. 196—198° (from ethyl acetate–methanol). Authentic methyl oleanolate, obtained by similar hydrolysis of its acetate, had m. p. 196—198° and there was no depression in m. p. on admixture.

Sapogenin II was converted into the acetate methyl ester, m. p. *ca.* 203°, in the usual way and the product subjected to prolonged fractional crystallisation (with triangulation) from ethyl acetate–methanol. After nine steps in the triangulation (32 fractions) methyl morolate acetate was isolated having m. p. 259—261°, $[\alpha]_D$ +39° (*c*, 4·04), mixed m. p. 261—263° with authentic material (see above), and also methyl oleanolate acetate, m. p. 218°, likewise undepressed in m. p. on admixture with an authentic specimen. No other substance could be isolated. A mixture of equal amounts of morolic and oleanolic acids, dissolved in a little dioxan and precipitated with water, had m. p. 262—267°, mixed m. p. with sapogenin II 268—273°. Recrystallisation of the mixture from ethanol afforded material of m. p. 268—270° closely resembling sapogenin II in appearance. A similarly prepared mixture of the corresponding acetate methyl esters had m. p. 202—203°.

Sapogenin III (2 g.) was converted into the (amorphous) acetate methyl ester in the usual way. Chromatography over alumina (Birlec; each fraction crystallised once from chloroform–methanol) gave the following fractions.

Fraction 1: Eluant 300 Ml., 1 : 1 light petroleum (b. p. 40—60°)–benzene; cryst., m. p. *ca.* 200°.
„ 2: „ 50 Ml., benzene; traces only.
„ 3: „ 30 Ml., benzene; 50 mg., cryst., m. p. 250—255°.
„ 4: „ 100 Ml., 1 : 1 benzene–ether; 20 mg., amorphous yellow solid, m. p. 230—250°.

Recrystallisation of fraction 1 gave methyl oleanolate acetate. Fractions 3 and 4 were not examined further.

Methyl Morolate Acetate Oxide.—(a) *Perbenzoic acid procedure* (cf. Table II). Methyl morolate acetate (1·07 g.) in dry chloroform (20 ml.) was treated with 1·31N-perbenzoic acid (5 ml.), also in chloroform, and left at 0°. After 20 hours 95% of the amount of per-acid required for one double bond

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* We are indebted to Mr. Campbell and Dr. Farmer for permission to quote their findings.

† The spent cloves were kindly placed at our disposal by Professor G. A. R. Kon, F.R.S., to whom we are much indebted.

had been consumed; after 43 hours the titre remained unchanged at a value corresponding to 1·1 double bonds. The solution was worked up in the usual way to give *methyl morolate acetate oxide*, m. p. 288°, $[\alpha]_D$ +30° (*c*, 1·73), +30° (*c*, 2·59) (Found: C, 74·95; H, 9·85. $C_{33}H_{53}O_5$ requires C, 74·95; H, 9·9%). This substance crystallised from chloroform–methanol in two distinct crystalline forms. However, its homogeneity was established by triangulation, carried to seven stages, and by extensive chromatography.

(b) *Perhydrol–acetic acid procedure.* Methyl morolate acetate (0·75 g.) in acetic acid (100 ml.) was heated on the steam-bath and perhydrol (2 ml., Merck) added during half an hour. Heating was continued for a further 2 hours. Dilution with water, filtration, and crystallisation from chloroform–methanol gave the oxide (0·66 g.), m. p. 288°, identical with that obtained by procedure (a). This is by far the more convenient method of preparation.

Methyl Morolate Oxide.—Alkaline hydrolysis of the foregoing acetate afforded *methyl morolate oxide* which, recrystallised from ethyl acetate–methanol, had m. p. 216—218°, $[\alpha]_D$ +21° (*c*, 2·79), +21° (*c*, 2·09) (Found: C, 76·4; H, 10·0. $C_{31}H_{50}O_4$ requires C, 76·5; H, 10·35%).

Methyl Morolate Benzoate Oxide.—Methyl morolate benzoate in warm glacial acetic acid was treated with perhydrol as described in procedure (b) above. Recrystallisation from methanol afforded the corresponding *oxide*, m. p. 203—204°, $[\alpha]_D$ +43° (*c*, 4·58) (Found: C, 77·65; H, 9·6. $C_{38}H_{54}O_6$ requires C, 77·25; H, 9·2%).

Action of Ozone on Methyl Morolate Acetate.—The acetate methyl ester (700 mg.) in ethyl chloride (50 ml.) was treated with ozone at −60° for half an hour. No volatile products could be detected and 650 mg. of unchanged starting material was recovered. 650 Mg. treated in the same way in carbon tetrachloride at 0° for 1 hour gave 450 mg. of unchanged starting material and no volatile products. 450 Mg. ozonised in 20 ml. of carbon tetrachloride at room temperature for 6 hours gave no volatile products; the solid product, m. p. 270—275°, obtained by evaporation of the carbon tetrachloride was chromatographed as indicated below, each fraction being crystallised once from chloroform–methanol:

Fraction 1: Eluant 50 Ml., benzene; m. p. 273—276°.
„ 2: „ 50 Ml., benzene; m. p. 286—288°.
„ 3: „ 50 Ml., benzene; m. p. 285—287°.

Further elution gave only traces of material. Fractions 1, 2, and 3 weighed 290 mg. Fraction 2 gave no depression in m. p. on admixture with pure methyl morolate acetate oxide, m. p. 288°.

Chromic Acid Oxidation of Methyl Morolate Acetate.—The acetate methyl ester (1·75 g.) was dissolved in acetic acid (150 ml.) at 100°. Chromic anhydride (0·9 g.) in 90% (vol.) aqueous acetic acid (50 ml.) was added during half an hour and the heating continued for a further 1·5 hours. After being worked up in the usual way the oxidation product was separated into neutral and acid fractions. The latter was very small and amorphous and was not examined further. The neutral fraction was chromatographed over alumina with the results indicated below, each fraction being crystallised once from chloroform–methanol before the m. p. determination:

Fraction	Eluant.	Yield (mg.).	M. p.
1	50 Ml., benzene	500	255—257°
2	50 Ml., „	50	253—255
3	150 Ml., „	Traces	Amorphous
4	70 Ml., 5 : 95 ether–benzene	Small	*ca.* 200
5	70 Ml., „ „	50	245—247
6	140 Ml., 10 : 90 „	Small	278—280
7	70 Ml., 50 : 50 „	Traces	—
8	140 Ml., ether	—	—

Recrystallisation of fractions 1 and 2 afforded unchanged starting material. Fraction 6 depressed the m. p. of methyl morolate acetate oxide to 240—250° and was not investigated further. Recrystallisation of fraction 5 from methanol afforded the O_7 acetate, m. p. 247—248°, $[\alpha]_D$ +31° (*c*, 0·89) (Found: C, 71·0; H, 8·45. Calc. for $C_{33}H_{46}O_7$: C, 71·45; H, 8·35%). An authentic specimen of the O_7 acetate, prepared from methyl dehydro-oleanolate acetate by the method of Mower, Green, and Spring (*J.*, 1944, 256), had m. p. 248—249° and gave no depression in m. p. on admixture with the product described above.

Moradiol.—(a) *From methyl morolate.* Methyl morolate (1·0 g.) in dry ether (100 ml.) was mixed with lithium aluminium hydride (0·5 g.) in dry ether. After being left at room temperature for 10 minutes with occasional shaking, the mixture was worked up by acidification with aqueous acetic acid, etc., in the usual way. The reaction product, recrystallised from methanol, furnished beautiful long flat needles (615 mg.), m. p. 220°, $[\alpha]_D$ −11° (*c*, 1·61), of pure *moradiol* (Found: C, 81·25; H, 11·2. $C_{30}H_{50}O_3$ requires C, 81·4; H, 11·4%). Further batches were prepared with equal facility from the acetate methyl ester. In each case the yield of pure product was 60—70%.

(b) *From morolic acid.* Morolic acid (4·2 g.) in dry ether (1 l.) was treated with 0·31M-ethereal lithium aluminium hydride (350 ml.). The mixture was left overnight and then refluxed gently for 2 hours. Working up in the usual way gave pure moradiol (2 g.), m. p. 220°, and *ca.* 0·5 g. of recovered morolic acid. This is the less satisfactory method of preparation.

Moradiol (200 mg.) in dry ether was treated with excess of lithium aluminium hydride in ether and the suspension refluxed for 48 hours. Working up in the usual way gave 160 mg. of unchanged moradiol.

Moradiol Diacetate.—Moradiol, refluxed in benzene solution with excess of acetic anhydride for 1 hour and worked up in the usual way, afforded *moradiol diacetate* which, recrystallised from chloroform–methanol, had m. p. 273°, $[\alpha]_D$ +23° (*c*, 2·46) (Found: C, 76·2; H, 10·3. $C_{34}H_{54}O_4.0{\cdot}5CH_3{\cdot}OH$ requires

C, 76·3; H, 10·4%). It gave a pink colour, deepening to a permanent red, in the Liebermann–Burchard reaction.

Moradiol 2-Monoacetate.—Moradiol diacetate (1·59 g.) was refluxed with ethanol (50 ml.) and 0·023N-potassium hydroxide (in dioxan–ethanol) (150 ml.) for 2 hours, 2 ml. of water being added during this period. After working up of the mixture by dilution with water and extraction with chloroform 795 mg. of pure *moradiol 2-monoacetate* were obtained, which, recrystallised from chloroform–methanol, had m. p. 282—283°, $[\alpha]_D$ +5° (*c*, 1·88) (Found: C, 78·8; H, 10·5. $C_{32}H_{52}O_3$ requires C, 79·3; H, 10·8%). In the Liebermann–Burchard reaction the monoacetate gave a pink colour, deepening to a permanent red colour.

Moradiol Diacetate Oxide.—Moradiol diacetate (500 mg.), dissolved in warm glacial acetic acid (75 ml.), was heated on the steam-bath for 30 minutes whilst perhydrol (Merck; 2 ml.) in acetic acid (10 ml.) was added. A further hour's heating, dilution with water, filtration, and recrystallisation of the product from chloroform–methanol gave *moradiol diacetate oxide* (460 mg.), m. p. 253—255°. Repeated recrystallisation raised the m. p. to 255—256°, $[\alpha]_D$ +17° (*c*, 10·0) (Found: C, 75·4; H, 9·9. $C_{34}H_{54}O_5$ requires C, 75·25; H, 10·0%). A further experiment with 1·8 g. of moradiol diacetate furnished 1·66 g. of the oxide.

Moradiol 2-Monoacetate Toluene-p-sulphonate.—To the 2-monoacetate (220 mg.) in dry pyridine (2 ml.) and dry benzene (3 ml.) toluene-*p*-sulphonyl chloride (200 mg.) was added and the solution refluxed for 5 hours. Working up in the usual way furnished the required *ester* which, recrystallised from chloroform–methanol, had m. p. 184° (decomp.) (Found: C, 74·1; H, 9·45. $C_{39}H_{58}O_5S$ requires C, 73·3; H, 9·15%). This ester (100 mg.) was reduced by lithium aluminium hydride according to the directions of Schmid and Karrer (*Helv. Chim. Acta*, 1949, **32**, 1371) for cholesteryl toluene-*p*-sulphonate. The only product was moradiol, m. p. 218°, mixed m. p. with pure diol (m. p. 220°) 220°.

Chromic Acid Oxidation of Moradiol.—Several experiments were carried out. In each the reaction product was heterogeneous and could only be separated into its components by careful chromatography. The most easily eluted substance [from alumina by 50 : 50 light petroleum (b. p. 40—60°)–benzene], recrystallised from chloroform–methanol, had m. p. 174—175°, $[\alpha]_D$ +95° (*c*, 1·66) (Found: C, 83·85; H, 11·15. Calc. for $C_{32}H_{48}O$: C, 84·8; H, 11·3%), not depressed in m. p. on admixture with authentic oleanone, m. p. 174—176°, $[\alpha]_D$ +96° (*c*, 3·08), prepared by chromic acid oxidation of oleanol according to the directions of Winterstein and Stein (*Annalen*, 1933, **502**, 223), followed by chromatography. The identity was confirmed by the preparation of the corresponding 2 : 4-dinitrophenylhydrazones. In both cases purification was effected by chromatography. Authentic *oleanone 2 : 4-dinitrophenylhydrazone*, recrystallised from chloroform–methanol, had m. p. 245—246° (Found: N, 9·2, 9·8. $C_{38}H_{50}O_4N_4$ requires N, 9·5%), and mixed m. p. 245—246°, with the 2 : 4-dinitrophenylhydrazone, m. p. 245—246°, prepared from the moradiol oxidation product.

A typical oxidation experiment was as follows: Moradiol (1·93 g.) in 1 : 4 ether–acetic acid (500 ml.) was treated dropwise with chromic anhydride (880 mg.) in 95% aqueous acetic acid (125 ml.) during 2 hours. After being left overnight the solution was worked up by dilution with water, ether extraction, etc., in the usual way. The partly crystalline reaction product was chromatographed over 60 g. of alumina with the following results, each fraction being crystallised once from chloroform–methanol:

Fraction.	Eluant.	Product.
1	1000 Ml., 50 : 50 light petroleum (b. p. 40—60°)–benzene	Contained the oleanone (see above)
2	50 Ml., 70 : 30 light petroleum (b. p. 40—60°)–benzene	Cryst., m. p. 175—192°
3	50 Ml., " "	Cryst. (main fraction), m. p. 180—194°, $[\alpha]_D$ +85° (*c*, 5·14)
4	50 Ml., " "	Cryst., m. p. 175—194°
5	50 Ml., " "	Cryst., m. p. 175—190°, $[\alpha]_D$ +88° (*c*, 2·06)
6	50 Ml., " "	Cryst., m. p. 167—182°, $[\alpha]_D$ +87° (*c*, 2·04)
7	100 Ml., " "	Cryst., m. p. 182—195°
8	50 Ml., " "	Trace, m. p. 160—180°
9	200 Ml., benzene	Nothing
10	200 Ml., 5 : 95 ether–benzene	Trace, oil
11	150 Ml., 25 : 75 "	"
12	50 Ml., " "	Cryst., m. p. 176—195°, $[\alpha]_D$ +41° (*c*, 2·42)
13	50 Ml., " "	Cryst., m. p. 160—162°, $[\alpha]_D$ +41° (*c*, 3·10)
14	50 Ml., " "	Cryst., m. p. 175—185°, $[\alpha]_D$ +33° (*c*, 4·17)
15	50 Ml., " "	Cryst., m. p. 185—192°
16	50 Ml., " "	Trace, cryst., m. p. 182—192°
17	100 Ml., ether	Cryst., m. p. 196—197°, $[\alpha]_D$ +26° (*c*, 2·30)
18	150 Ml., 1 : 1-chloroform—methanol	Cryst., m. p. 215—218°

Fractions 5—7, combined and recrystallised from chloroform–methanol, gave *moronal*, m. p. 185—200° (indefinite), $[\alpha]_D$ +88° (*c*, 3·48) (Found: C, 81·5; H, 10·6. $C_{30}H_{46}O_2$ requires C, 82·1; H, 10·6%). The orange *bis-2 : 4-dinitrophenylhydrazone*, prepared in the usual way and purified by chromatography followed by recrystallisation from chloroform–methanol, melted sharply at 240—241° (Found: N, 14·2. $C_{42}H_{54}O_8N_8$ requires N, 14·05%).

Repeated recrystallisation of fraction 17, without change in m. p., gave what was probably *moronol*, m. p. 196—197° (Found: C, 81·4; H, 11·0. $C_{30}H_{48}O_2$ requires C, 81·75; H, 11·0%).

Fraction 12 was heterogeneous since two recrystallisations from chloroform–methanol changed the

specific rotation to +77° (*c*, 0·84). Acetylation gave somewhat impure acetoxymoral, $[\alpha]_D$ +57° (*c*, 1·81) (see below).

Fractions corresponding to 12, 13, 14 and 15 were obtained in a number of other oxidations and, in each case, it was not possible to isolate a pure compound by direct recrystallisation. However acetylation of such fractions by pyridine–acetic anhydride, followed by careful chromatography, gave acetoxymoral, m. p. 250—260°, $[\alpha]_D$ +62° (*c*, 2·60).

Fraction 18 was somewhat impure moradiol.

In one experiment a further unidentified compound was obtained. It was eluted from alumina with 1 : 1 ether–benzene and, after recrystallisation from chloroform–methanol, melted sharply at 168°, $[\alpha]_D$ + 39° (*c*, 3·67) (Found : C, 80·15; H, 11·15%). Further recrystallisation did not alter the m. p. It was not investigated further.

Chromic Acid Oxidation of Moradiol 2-Monoacetate.—The monoacetate (663 mg.) in acetic acid (200 ml.) and ether (500 ml.) was oxidised by dropwise addition of chromic anhydride (150 mg.) in 97% aqueous acetic acid (15 ml.) during 45 minutes. The solution was left for 3 hours and then worked up in the usual way. The crystalline reaction product was chromatographed over 40 g. of alumina, each fraction being crystallised once from chloroform–methanol :

Fraction.	Eluant.	Product.
1	300 Ml., 80 : 20 light petroleum (b. p. 40—60°)–benzene	Trace only
2	200 Ml., 70 : 30 light petroleum (b. p. 40—60°)–benzene	Cryst., m. p. *ca.* 205°
3	100 Ml., ,, ,,	Nil
4	50 Ml., ,, ,,	Cryst., m. p. 255—260°
5	50 Ml., 60 : 40 light petroleum (b. p. 40—60°)–benzene	Cryst., m. p. 255—265°
6	100 Ml., ,, ,,	Cryst., m. p. 255—265°
7	200 Ml., ,, ,,	Cryst., trace
8	200 Ml., 40 : 60 light petroleum (b. p. 40—60°)–benzene	Nil
9	180 Ml., benzene	,,
10	50 Ml., 1 : 1 ether–benzene	,,
11	50 Ml., ,, ,,	Cryst., m. p. 247—248°
12	50 Ml., ,, ,,	Cryst., m. p. 260—270°

Fraction 2 was clearly identical with oleanyl acetate (see below). Fractions 4—6, recrystallised from chloroform–methanol, had $[\alpha]_D$ +63° (*c*, 2·39). After further recrystallisation the m. p. remained indefinite, but the specific rotation remained constant, $[\alpha]_D$ +62° (*c*, 2·68). Clearly these fractions consisted of *acetoxymoral* (Found : C, 80·0, 79·0; H, 10·7, 10·3. $C_{32}H_{50}O_3$ requires C, 79·6; H, 10·45%). The corresponding 2 : 4-*dinitrophenylhydrazone*, prepared in the usual way and purified by chromatography, melted sharply at 243° (Found : N, 8·85. $C_{38}H_{54}O_6N_4$ requires N, 8·45%).

Fraction 11, recrystallised from chloroform–methanol, gave a *substance*, m. p. 247—249°, $[\alpha]_D$ +40° (*c*, 1·30) (Found : C, 79·2; H, 10·65. $C_{32}H_{52}O_3$ requires C, 79·3; H, 10·8%). It was not investigated further. Fraction 12, on recrystallisation from chloroform–methanol, had m. p. 274—279°, $[\alpha]_D$ +12° (*c*, 1·80), and was shown to be somewhat impure starting material.

Morene (*Germanicene*).—Moronal (250 mg.) in the minimum of absolute ethanol was refluxed with several times the theoretical amount of 94% hydrazine for 2 hours. Concentration of the ethanolic solution furnished crude moronal dihydrazone, which (130 mg.) with 94% hydrazine (2 ml.) and a solution of sodium (250 mg.) in ethanol (6 ml.) was heated at 180° overnight. The reaction mixture was worked up in the usual way. Chromatography over alumina furnished in the first light petroleum (b. p. 40—60°) eluate morene (germanicene) (40 mg.); recrystallised from chloroform–methanol, this had m. p. 171—172°, $[\alpha]_D$ +3° (*c*, 0·60) (Found : C, 87·45; H, 12·3. Calc. for $C_{30}H_{50}$: C, 87·75; H, 12·25%).

Morol (*Germanicol*).—The crude hydrazone (80 mg.) of acetoxymoral, prepared as for moronal, was heated for 12 hours at 180° with 94% hydrazine (2 ml.) and a solution of ethanolic sodium ethoxide (250 mg. of sodium in 6 ml. of absolute ethanol). The reaction mixture was worked up in the usual way to give a crude product, m. p. *ca.* 150°. Acetylation with excess of acetic anhydride in pyridine on the water-bath for 2 hours and working up in the usual way gave a crystalline substance, m. p. 259—262°, depressed in m. p. by admixture with moradiol diacetate. Careful chromatography, over 10 g. of alumina, of this and the product of a further Wolff–Kishner reduction, gave the following results, each fraction being crystallised once from chloroform–methanol :

Fraction.	Eluent.	Product.
1	100 Ml., 90 : 10 light petroleum (b. p. 40—60°)–benzene	Plates, m. p. 267—270°
2	150 Ml., ,, ,,	Nil
3	50 Ml., 50 : 50 light petroleum (b. p. 40—60°)–benzene	Plates, m. p. 264—269°

Fraction 1, the main fraction, consisted of moryl acetate and had, on recrystallisation from ethyl acetate–methanol, m. p. 268—270°, $[\alpha]_D$ +18° (*c*, 1·13). It gave no depression in m. p. with an authentic specimen of germanicyl acetate, m. p. 269—271°, $[\alpha]_D$ recorded (Simpson, *J.*, 1944, 283) as +18°.

Fraction 3 gave no depression in m. p. on admixture with morodiol diacetate m. p. 273°.

Alkaline hydrolysis of moryl acetate gave morol (recrystallised from methanol), m. p. 173—175°, $[\alpha]_D$ +4° (*c*, 4·78). There was no depression in m. p. on admixture with an authentic specimen of germanicol, m. p. 171—173°, $[\alpha]_D$ +4° (*c*, 3·24).

Benzoylation of morol by heating with benzoyl chloride in pyridine solution on the steam-bath for

several hours, and then working up in the usual way, afforded moryl benzoate (recrystallised from chloroform–methanol), m. p. 261—262°, $[\alpha]_D$ +38° (*c*, 2·86). Germanicyl benzoate, prepared from germanicol in the same way and recrystallised from chloroform–methanol, had m. p. 261—262°, $[\alpha]_D$ + 37° (*c*, 4·31), and there was no depression in m. p. on admixture with moryl benzoate.

In the Liebermann–Burchard reaction morol behaved in the same way as methyl morolate acetate.

Oxide Fission by Dry Hydrogen Chloride.—(*a*) Methyl morolate acetate oxide (200 mg.) in chloroform (200 ml.) was treated for 30 minutes at room temperature with a stream of dry hydrogen chloride. Removal of the solvent *in vacuo* and recrystallisation of the residue from chloroform–methanol yielded needles (160 mg.), m. p. 220—221°, $[\alpha]_D$ −127° (*c*, 4·59). An authentic specimen of methyl dehydro-oleanolate acetate, prepared according to the procedure of Ruzicka *et al.* (*Helv. Chim. Acta*, 1939, **22**, 788) and recrystallised from chloroform–methanol, had m. p. 220—221°, $[\alpha]_D$ −128° (*c*, 4·49), −127° (*c*, 3·50). Identity was confirmed by a mixed m. p. which showed no depression.

(*b*) Methyl morolate benzoate oxide (220 mg.) in chloroform (20 ml.) was treated as under (*a*) above. The product (150 mg.), recrystallised from chloroform–methanol, had m. p. 282—283°, $[\alpha]_D$ −95° (*c*, 3·35). There was no depression in m. p. on admixture with authentic *methyl dehydro-oleanolate benzoate* (recrystallised from chloroform–methanol), m. p. 281—282°, $[\alpha]_D$ −93° (*c*, 4·12) (Found: C, 79·4; H, 9·3. $C_{38}H_{52}O_4$ requires C, 79·65; H, 9·15%). The latter was prepared by heating the corresponding alcohol (see below) in pyridine with excess of benzoyl chloride on the steam-bath for 3 hours and then working up the product in the usual way.

A portion of the benzoate, prepared from the oxide, was hydrolysed by alkali to the corresponding alcohol, m. p. 168° (from methanol), $[\alpha]_D$ −137° (*c*, 3·95). There was no depression in m. p. on admixture with methyl dehydro-oleanolate (recrystallised from methanol), m. p. 168°, $[\alpha]_D$ −139° (*c*, 5·16), prepared by alkaline hydrolysis of the acetate.

Oxide Fission by Aqueous-methanolic Sulphuric Acid.—Methyl morolate acetate oxide (106 mg.) was refluxed for 24 hours with 95% methanol (50 ml.) to which 2N-aqueous sulphuric acid (5 ml.) had been added. The solution was evaporated to two-thirds of its bulk, poured into water (200 ml.), and extracted with ether. The product, recrystallised from aqueous acetone, afforded pure *methyl* iso*dehydro-oleanolate* (55 mg.), m. p. 179—180°, $[\alpha]_D$ +214° (*c*, 2·50) ($\lambda_{max.}$ 237 mμ.; ε = 10,200) (Found: C, 79·5; H, 10·7. $C_{31}H_{48}O_3$ requires C, 79·45; H, 10·3%).

The mother-liquors from a similar preparation were evaporated to dryness and the residue acetylated by dissolving it in pyridine, adding excess of acetic anhydride, and leaving the mixture for 2 days at room temperature. After being worked up in the usual way the reaction product was chromatographed over alumina, to give pure *methyl* iso*dehydro-oleanolate acetate* which, recrystallised from ethyl acetate–methanol, had m. p. 195°, $[\alpha]_D$ +209° (*c*, 3·35) (Found: C, 77·9; H, 10·05. $C_{33}H_{50}O_4$ requires C, 77·6; H, 9·85%).

The above-mentioned acetate methyl ester (600 mg.) was heated with 20 ml. of 85% ethanol containing 20% of potassium hydroxide at 170° for 6 hours. After working up of the acid fraction in the usual way and recrystallisation from aqueous methanol, iso*dehydro-oleanolic acid*, m. p. 232—233° (decomp.), $[\alpha]_D$ +224° [$\lambda_{max.}$ 229 and 238 mμ.; ε (both) = 8200], was obtained (Found: C, 77·9; H, 10·45. $C_{30}H_{44}O_3$, $0{\cdot}5CH_3{\cdot}OH$ requires C, 77·8; H, 10·3%).

The pure acetate methyl ester (40 mg.) in acetic acid (25 ml.) was hydrogenated over platinum oxide catalyst (20 mg.) for 24 hours, until there was no further absorption. Working up the product in the usual way and recrystallisation from chloroform–methanol gave crystals, m. p. 229—232°, not depressed by admixture with a specimen of authentic methyl olean-13(18)-enolate acetate, m. p. 230—231°, prepared according to the method of Jeger, Norymberski, and Ruzicka (*Helv. Chim. Acta*, 1944, **27**, 1532).

Methyl *iso*dehydro-oleanolate acetate (100 mg.) in chloroform (20 ml.) was treated with a stream of dry hydrogen chloride for 15 minutes at room temperature. Working up in the usual way and recrystallisation from chloroform–methanol afforded, in almost quantitative yield, methyl dehydro-oleanolate acetate, m. p. 219—221°, not depressed by admixture with an authentic specimen m. p. 220—221°.

Oxidation of Methyl Morolate Acetate by Selenium Dioxide.—To the acetate methyl ester (500 mg.) in acetic acid (50 ml.) selenium dioxide (250 mg.) was added and the solution refluxed for 6 hours. Worked up in the usual way the reaction product was obtained as an oil. It was chromatographed over 30 g. of alumina, each solid fraction being crystallised once from chloroform–methanol:

Fraction.	Eluant.	Product.
1	200 Ml., 75 : 25 light petroleum (b. p. 40—60°)–benzene	Nil
2	50 Ml., 50 : 50 light petroleum (b. p. 40—60°)–benzene	Cryst., m. p. 192°
3	50 Ml., " "	Cryst., m. p. 193°
4	100 Ml., " "	Trace
5	50 Ml., benzene	Cryst., m. p. 249—252° (decomp.)
6	50 Ml., benzene	Trace
7	50 Ml., 5 : 95 ether–benzene	Trace, amorphous

Fractions 2 and 3, combined and recrystallised from chloroform–methanol, gave methyl *iso*dehydro-oleanolate acetate, m. p. 193—194°, $[\alpha]_D$ +210° (*c*, 3·35), not depressed on admixture with an authentic specimen m. p. 195°.

Fraction 5 gave a 30° depression in m. p. on admixture with methyl diketo-oleandienolate acetate (m. p. 245—246°, $[\alpha]_D$ −146°) prepared according to the directions of Ruzicka *et al.* (*Helv. Chim. Acta*, 1939, **22**, 788). It was not investigated further.

Pyrolysis of Morolic Acid.—Morolic acid (2 g.) was heated at the m. p. in a fused mixed-nitrite bath.

As the acid melted, carbon dioxide was evolved; there was no further evolution of gas on continued heating. After 5 minutes the melt was rapidly cooled, whereupon it crystallised. One crystallisation from chloroform–methanol gave needles (1·65 g.), m. p. 222—224°, $[\alpha]_D$ +56° (*c*, 5·76). There was no depression in m. p. on admixture with an authentic specimen of oleanol (recrystallised from chloroform–methanol), m. p. 221—224°, $[\alpha]_D$ +56° (*c*, 1·49), prepared by pyrolysis of oleanolic acid according to the directions of Winterstein and Stein (*Z. physiol. Chem.*, 1931, **202**, 222).

The product from the pyrolysis of the morolic acid was refluxed with excess of acetic anhydride for 30 minutes. Working up in the usual way and recrystallisation from chloroform–methanol afforded the acetate, m. p. 201—203°, $[\alpha]_D$ +48° (*c*, 2·51). There was no depression in m. p. on admixture with oleanyl acetate, m. p. 201—204°, $[\alpha]_D$ +47° (*c*, 3·03), prepared in the same way from authentic oleanol.

Pyrolysis of Olean-13(18)-enolic Acid.—Methyl olean-13(18)-enolate acetate was heated at 180° in 85% ethanol (15 ml.) containing 20% of potassium hydroxide for 8 hours. Working up in the usual way furnished, in the acid fraction, *olean-13(18)-enolic acid* which, recrystallised from methanol, had m. p. 252—254° (decomp.) (Found: C, 75·35; H, 11·3. $C_{30}H_{48}O_3,CH_3{\cdot}OH$ requires C, 76·2; H, 10·7%). When heated at 270° for 1 minute, the acid (50 mg.) melted with effervescence. Recrystallisation of the cooled crystalline melt from methanol furnished crystals (35 mg.), m. p. 220—222° not depressed on admixture with authentic oleanol of m. p. 222—224°. Olean-13(18)-enolic acid was recovered unchanged under conditions adequate for the formation of a bromo-lactone from oleanolic acid (Winterstein and Stein, *Z. physiol. Chem.*, 1931, **199**, 56, 64).

Pyrolysis of iso*Dehydro-oleanolic Acid.*—The acid (350 mg.) was heated at 230° for 5 minutes and then at 240° for 5 minutes. The cooled melt was chromatographed over alumina, to furnish three fractions of *norolean*-12 : 18(17)-*dienol* which, recrystallised from methanol, had m. p. 189—191°, $[\alpha]_D$ +79° (*c*, 3·72) (Found: C, 84·7; H, 11·4. $C_{29}H_{44}O$ requires C, 84·8; H, 11·3%). Acetylation on the steam-bath for 2 hours with an excess of acetic anhydride in pyridine and then working up in the usual way gave *norolean*-12 : 18(17)-*dienol acetate* which, recrystallised from ethyl acetate–methanol, had m. p. 187—188°, $[\alpha]_D$ +66° (*c*, 3·66) ($\lambda_{max.}$ 238 and 244 mμ.; ε = 16,700 and 18,800 respectively) (Found: C, 81·3; H, 10·65. $C_{31}H_{46}O_2$ requires C, 82·05; H, 10·65%).

A specimen of norechinocystadienol, kindly supplied by Professor C. R. Noller (Stanford), had m. p. 189—191°, not depressed on admixture with norolean-12 : 18(17)-dienol, also of m. p. 189—191°. Acetylation of norechinocystadienol by treatment with an excess of acetic anhydride in pyridine at room temperature for 24 hours and then working up in the usual way gave the acetate which, recrystallised from methanol, had m. p. 175—178°. After three further recrystallisations the m. p. was 178—180° after sintering at 172° and was not depressed on admixture with norolean-12 : 18(17)-dienol acetate. Fractional crystallisation from aqueous methanol of the more soluble portion of the norechinocystadienol acetate finally gave an acetate, m. p. 186—188°, mixed m. p. with norolean-12 : 18(17)-dienol acetate also 186—188°.

Norolean-12 : 18(17)-dienol (100 mg.) was heated on the steam-bath with excess of benzoyl chloride in pyridine for 2 hours. Working up in the usual way afforded *norolean*-12 : 18(17)-*dienol benzoate*; recrystallised from chloroform–methanol, this had m. p. 227—229°, $[\alpha]_D$ +80° (*c*, 1·50) (Found: C, 83·95; H, 9·85. $C_{36}H_{46}O_2$ requires C, 84·0; H, 9·8%).

Reduction of Moradiol Diacetate Oxide by Lithium Aluminium Hydride.—Moradiol diacetate oxide (1·6 g.) in dry ether (700 ml.) was treated with a large excess of lithium aluminium hydride in ether, and the mixture was refluxed for 20 hours. The excess of hydride was destroyed by aqueous acetic acid, and the ethereal layer was separated, washed, and evaporated, yielding a crystalline residue. This sintered at 180° and melted with decomposition at 200—208°. It was acetylated by heating it in pyridine on the steam-bath for 1·5 hours with an excess of acetic anhydride. The crude acetate, worked up as usual, was chromatographed over alumina, each fraction being crystallised once from chloroform–methanol:

Fraction.	Eluant (50 ml.).	Product.
1	Benzene	*ca.* 100 Mg., m. p. 215—218°
2	,,	*ca.* 250 Mg., m. p. 212—216
3	,,	*ca.* 100 Mg., m. p. 184—188
4	,,	*ca.* 50 Mg., m. p. 233—238
5	95 : 5 Benzene–ether	*ca.* 20 Mg., m. p. 243—246

Further elution with benzene–ether and chloroform–methanol afforded only traces of oils.

Fractions 1 and 2, combined and recrystallised several times from chloroform–methanol, furnished fine needles (260 mg.) of *norolean*-16 : 18-*dienol acetate*, m. p. 220—222°, $[\alpha]_D$ −19° (*c*, 2·95) ($\lambda_{max.}$ 241 mμ.; ε = 17,200) (Found: C, 81·9; H, 10·8. $C_{31}H_{46}O_2$ requires C, 82·05; H, 10·65%). The Liebermann–Burchard reaction was red changing to yellow.

Fractions 4 and 5, together with their respective mother-liquors, were combined and re-chromatographed over alumina, each fraction being crystallised once from chloroform–methanol:

Fraction.	Eluant (50 ml.).	Product, m. p.	Fraction.	Eluant (50 ml.).	Product, m. p.
6	1 : 1 Light petroleum (b. p. 40—60°)–benzene	212—215°	10	1 : 1 Light petroleum (b. p. 40—60°)–benzene	243—245°
7	,, ,,	212—218	11	,, ,,	245—247
8	,, ,,	190—210	12	Benzene (200 ml.)	Trace
9	,, ,,	243—245 (main fraction)			

Fractions 9—11 inclusive were combined and recrystallised from chloroform–methanol. The *acetate* (p. 265) had the constant m. p. 248—250°, $[\alpha]_D$ −2° (*c*, 2·28) (Found: C, 79·6; H, 10·5. $C_{32}H_{50}O_3$ requires C, 79·6; H, 10·45%). It gave a yellow colour with tetranitromethane. In the Liebermann–Burchard reaction the colour sequence was red changing to deep reddish-violet.

Alkaline hydrolysis of norolean-16 : 18-dienol acetate in the usual way afforded *norolean*-16 : 18-*dienol* which, recrystallised from chloroform–methanol, had m. p. 181—183°, $[\alpha]_D$ −45° (*c*, 1·84) (Found: C, 84·0; H, 11·4. $C_{28}H_{46}O$ requires C, 84·8; H, 11·3%).

Norolean-16 : 18-dienol acetate (50 mg.) in chloroform (20 ml.) was treated at room temperature with a stream of dry hydrogen chloride. Removal of the solvent *in vacuo* and recrystallisation of the residue from chloroform–methanol furnished norolean-12 : 18(17)-dienol acetate, m. p. 187—189°, $[\alpha]_D$ +68° (*c*, 3·41), not depressed by admixture with an authentic specimen.

The acetate (10 mg.) of m. p. 248—250°, $[\alpha]_D$ −2°, in chloroform (5 ml.) was treated with a stream of dry hydrogen chloride for 15 minutes. Removal of the solvent *in vacuo* and recrystallisation of the residue from methanol gave norolean-12 : 18(17)-dienol acetate, m. p. 188—189°, undepressed in m. p. on admixture with an authentic specimen.

50 Mg. each of norolean-16 : 18-dienol acetate and oleanolic acid were fused together over a free flame. The melt was kept at 250° for 15 minutes. After cooling the product was chromatographed over alumina and recrystallised from methanol, to give nearly 40 mg. of unchanged norolean-16 : 18-dienol acetate, m. p. 217—219°, undepressed on admixture with the starting material.

Reduction of Methyl Morolate Acetate Oxide by Lithium Aluminium Hydride.—The oxide (1·0 g.) in dry ether (1·7 l.) was treated with an excess of lithium aluminium hydride in ether, and the solution refluxed on the steam-bath for 20 hours. The product was worked up as for the reduction of the moradiol diacetate oxide except that acetylation was carried out at room temperature for 24 hours. Chromatography over alumina gave the following fractions, each recrystallised once from chloroform–methanol:

Fraction.	Eluant (70 ml.).	Product, m. p.	Fraction.	Eluant (70 ml.).	Product, m. p.
1	1 : 1 Light petroleum (b. p. 40—60°)–benzene	219—221°	5	1 : 1 Light petroleum (b. p. 40—60°)–benzene	195—235°
2	,, ,,	214—218	6	95 : 5 Benzene–ether	235—245
3	,, ,,	170—183	7	—	250—253
4	,, ,,	173—176	8	90 : 10 Benzene–ether	252—254

Fraction 2, recrystallised, had m. p. 219—221°. Combined with fraction 1 and recrystallised once more it gave 310 mg. of norolean-16 : 18-dienol acetate, m. p. 220—222°, not depressed on admixture with the preparation from moradiol diacetate oxide.

Fractions 7 and 8, recrystallised from chloroform–methanol, had m. p. 254—256°, not depressed by admixture with moradiol diacetate oxide.

Fractions 3, 4, and 5 were combined and carefully re-chromatographed. It was not possible, however, to isolate any of the compound of m. p. 248—250°, $[\alpha]_D$ −2° (see above), and all fractions of the chromatogram gave large depressions in m. p. on admixture with this compound.

Norolean-16 : 18-*dienol Acetate from Siaresinolic Acid.*—2-Hydroxy-19-keto-olean-13(18)-en-17-oic acid (1·1 g.), m. p. 290—300° (decomp.), prepared from siaresinolic acid (obtained from Siamese gum benzoin according to the procedure of Winterstein and Egli, *Z. physiol. Chem.*, 1931, **202**, 207) by the method of Bilham, Kon, and Ross (*J.*, 1942, 540), was heated for 1 minute in an air-bath at 310°. On cooling, a brittle resin was obtained. This was dissolved in pyridine and heated on the steam-bath for 1 hour with an excess of acetic anhydride. After working up in the usual way the product was chromatographed over alumina. Elution of the column with benzene furnished 2-*acetoxynorolean*-17-*en*-19-*one* (250 mg.) which, recrystallised from methanol, had m. p. 232—233°, $[\alpha]_D$ +137° (*c*, 3·11), +139° (*c*, 1·31) ($\lambda_{max.}$ 248 mμ.; ε = 8400) (Found: C, 79·8; H, 10·8. $C_{31}H_{48}O_3$ requires C, 79·45; H, 10·3%).

This nor-ketone (100 mg.) in dry ether (100 ml.) was reduced by an excess of lithium aluminium hydride in ether, the solution being refluxed for 2 hours. The excess of the reducing agent was destroyed by aqueous acetic acid, and the ethereal layer separated and washed with sodium hydrogen carbonate solution. Evaporation gave a residue which, recrystallised, after azeotropic drying with benzene, from chloroform–light petroleum (b. p. 40—60°), melted unsharply at *ca.* 201° (decomp.) and had $[\alpha]_D$ +18° (*c*, 0·51). On further recrystallisation from the same solvent mixture the m. p. remained indefinite and finally fell to 170—180° (decomp.).

The reduction product (50 mg.) was heated in pyridine on the water-bath with excess of acetic anhydride for 2 hours. After working up in the usual way and one recrystallisation from methanol, needles were obtained, having $[\alpha]_D$ −17° (*c*, 1·98), m. p. 216—218°, not depressed on admixture with norolean-16 : 18-dienol acetate. The acetylated product was chromatographed over alumina, each fraction being crystallised once from methanol:

Fraction.	Eluant.	Product, m. p.
1	25 Ml., 75 : 25 light petroleum (b. p. 40—60°)–benzene	218—220°
2	50 Ml., ,, ,,	220—222 (main fraction)
3	50 Ml., 50 : 50 light petroleum (b. p. 40—60°)–benzene	217—219
4	100 Ml., ,, ,,	216—218 (trace)
5	100 Ml., Benzene	Nil

Fraction 2 weighed 32 mg. and gave no depression in m. p. on admixture with norolean-16 : 18-dienol acetate, m. p. 220—222°, prepared from morolic acid. Fractions 1, 3, and 4 combined weighed

8 mg. Fraction 2 was subjected to alkaline hydrolysis in the usual way. The reaction product, recrystallised from methanol, had m. p. 181—183° and gave no depression on admixture with norolean-16 : 18-dienol of the same m. p.

The experiment described above was repeated with 100 mg. of 2-acetoxynorolean-17-en-19-one, but the reduction product was acetylated at room temperature for 24 hours. The results were identical in all respects with those just recorded.

Alkaline hydrolysis of 2-acetoxynorolean-17-en-19-one (70 mg.) under the usual conditions furnished 2-*hydroxyolean*-17-*en*-19-*one* which, recrystallised from methanol, had m.p. 258° (50 mg.), $[\alpha]_D$ +143° (*c*, 3·77) (Found : C, 82·05; H, 11·2. $C_{29}H_{44}O_2$ requires C, 81·65; H, 10·85%).

Action of Perbenzoic Acid on Morolic Acid Acetate.—Morolic acid acetate consumed one equivalent of oxidant on treatment with excess of perbenzoic acid (cf. p. 258). Working up the product of this reaction proved unexpectedly complicated and we defer a full exposition of the experimental results until the constitution of one of the reaction products, originally found in the acid fraction, has been established.

Morolic acid acetate (1·1 g.) in chloroform (100 ml.) was treated with 1·145N-chloroformic perbenzoic acid (10 ml.) and left at 0° for 27 hours. It was then mixed with ether and water, and the acid fraction extracted with concentrated potassium hydroxide solution. The neutral fraction, washed with aqueous hydrochloric acid and then evaporated, was recrystallised from chloroform–methanol, to give norolean-16 : 18-dienol acetate (*ca.* 500 mg.), m. p. and mixed m. p. with an authentic specimen 220—222°.

2 : 28-*Dihydroxyolean*-13(18)-*ene.*—During the experiments described in this paper 2 : 28-dihydroxyolean-13(18)-ene and its diacetate were prepared for comparative purposes. It is our understanding that these two compounds were prepared by a different route by Professor E. R. H. Jones, F.R.S., at an earlier date and that their properties will be fully reported by him in a subsequent paper.

2 : 28-Dihydroxyolean-13(18)-ene, prepared by lithium aluminium hydride reduction of methyl olean-13(18)-enolate acetate and recrystallised from methanol (after purification through the diacetate, see below), had m. p. 269°, $[\alpha]_D$ −45° (*c*, 0·60) (Found : C, 78·6; H, 11·55. Calc. for $C_{30}H_{50}O_2.CH_3{\cdot}OH$: C, 78·4; H, 11·45%).

2 : 28-Diacetoxyolean-13(18)-ene, recrystallised from chloroform–methanol, had m. p. 194—195°, $[\alpha]_D$ −52° (*c*, 6·36), −55° (*c*, 5·47) (Found : C, 77·9; H, 10·35. Calc. for $C_{34}H_{54}O_4$: C, 77·5; H, 10·35%).

Pyrolysis of Oleanolic Lactone.—The lactone (200 mg.), prepared by a method which will be reported later, was heated at 300°, raised to 350° during 5 minutes. The resin obtained on cooling was acetylated with an excess of boiling acetic anhydride, and the product chromatographed over alumina. 90 : 10 Light petroleum (b. p. 40—60°)–benzene eluted 30 mg. of oleanol acetate, m. p. 197—201°. Alkaline hydrolysis afforded oleanol which, recrystallised from methanol, had m. p. 222—224°, not depressed on admixture with oleanol obtained by the pyrolysis of oleanolic acid.

Action of Hydrogen Chloride on Various Substances.—The following general procedure was adopted. The compound (200 mg.) in chloroform (20 ml.) was treated with a stream of dry hydrogen chloride for 30 minutes. The solvent was removed *in vacuo* and the residue recrystallised from chloroform–methanol or methanol. Morolic acid, morolic acid acetate, methyl olean-13(18)-enolate acetate, methyl oleanolate acetate, and oleanol were each recovered unchanged in almost quantitative yield.

Absorption Spectra of Steroidal Dienes.—(*a*) Dehydro-α-ergostenyl acetate, as prepared by Barton and Cox (*J.*, 1949, 214), had $\lambda_{max.}$ 248 mμ., ε = 19,800.

(*b*) For the absorption spectrum of ergosteryl D acetate see Barton and Cox, *J.*, 1949, 219.

(*c*) Ergosteryl B_3 acetate was prepared in the following way, which gives a purer product than that described in the literature (cf. Windaus *et al.*, *Annalen*, 1931, **488**, 91; Dithmar and Achtermann, *Z. physiol. Chem.*, 1932, **205**, 55). Ergosteryl acetate (3·0 g.) in chloroform (100 ml.) was treated with dry hydrogen chloride gas at −30° for 2 hours. The solution was poured, at once, into an excess of ice-cold sodium hydrogen carbonate solution. Extraction with ether, washing with water, and evaporation *in vacuo* gave a crude acetate, m. p. 123—125°. Several recrystallisations raised the m. p. to a constant value of 140—141°; $[\alpha]_D$ was then −221° (*c*, 0·70). Careful fractionation of this material revealed that it was pure ergosteryl B_3 acetate.

A better yield of the B_3 sterol acetate is obtained if purification is effected through the benzoate. Purified by recrystallisation from ethyl acetate–ethanol *ergosteryl* B_3 *benzoate* had m. p. 158—159°, $[\alpha]_D$ −187° (*c*, 2·24) (Found : C, 83·8; H, 9·35. $C_{35}H_{48}O_2$ requires C, 84·0; H, 9·6%). Alkaline hydrolysis and working up in the usual way afforded ergosterol B_3 which, recrystallised from ethyl acetate–methanol, had m. p. 139°, $[\alpha]_D$ −238° (*c*, 3·12). Acetylation in the usual way in pyridine solution gave ergosteryl B_3 acetate with the physical constants {$[\alpha]_D$ −220° (*c*, 2·13)} recorded above. It showed $\lambda_{max.}$ 242 mμ., ε = 9900.

The greater part of the work described above was carried out at Harvard University, Cambridge, Mass., during the tenure by one of us (D. H. R. B.) of a Visiting Lectureship for the 1949—50 session. We should like to express our best thanks for the hospitality extended to us during this period and to acknowledge our indebtedness to Professor and Mrs. L. F. Fieser, Professor R. B. Woodward, and many others at Harvard for stimulating discussion of the subject of this paper and of related topics. We thank the Government Grants Committee of the Royal Society and the Central Research Fund of London University for financial assistance.

Harvard University, Cambridge, Mass.
Birkbeck College Research Laboratory,
21, Torrington Sq., London, W.C.1.

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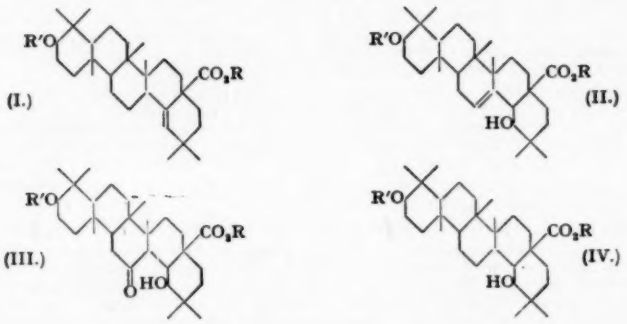
61. *Triterpenoids. Part II. The Partial Synthesis of Morolic Acid.*

By D. H. R. Barton, C. J. W. Brooks, and N. J. Holness.

Methyl morolate acetate (methyl olean-18-enolate acetate) has been obtained by a partial synthesis based on methyl siaresinolate acetate. The synthesis provides final confirmation of the formula assigned previously (Barton and Brooks, preceding paper) to morolic acid.

In Part I of this series (preceding paper) it was concluded that morolic acid, the characteristic triterpenoid sapogenin of *Mora excelsa*, Benth., was olean-18-enolic acid (I; R = R′ = H). To provide final confirmation for our views as to the structure of this acid, its partial synthesis from siaresinolic acid (II; R = R′ = H) (Bilham, Kon, and Ross, *J.*, 1942, 540; Ruzicka, Grob, Egli, and Jeger, *Helv. Chim. Acta*, 1943, **26**, 1218) was undertaken.

Treatment of methyl siaresinolate 2-acetate (II; R = Me, R′ = Ac) with perhydrol in acetic acid afforded, in a manner characteristic of the 12(13)-ethylenic linkage (*inter al.*, Ruzicka and Cohen, *ibid.*, 1937, **20**, 804; Ruzicka, Müller, and Schellenberg, *ibid.*, 1939, **22**, 758; Picard, Sharples, and Spring, *J.*, 1939, 1045; Picard and Spring, *J.*, 1940, 1387), methyl 12-keto-oleananolate acetate (III; R = Me, R′ = Ac). Wolff–Kishner reduction of this ketone (cf. Ruzicka and Jeger, *Helv. Chim. Acta*, 1941, **24**, 1178) furnished, after methylation and acetylation, methyl dihydrosiaresinolate acetate (IV; R = Me, R′ = Ac) which was smoothly dehydrated by phosphorus oxychloride in hot pyridine to give methyl olean-18-enolate acetate (I; R = Me, R′ = Ac). The latter was identical in all respects with authentic methyl morolate acetate.



Experimental.

M. p.s are uncorrected. Unless specified to the contrary rotations were determined for the sodium D line in chloroform solution at room temperature, which varied from 15° to 25°. For rotation measurements all specimens were dried *in vacuo* at 20° below the m. p. or at 110°, whichever was the lower. Values of $[\alpha]_D$ have been approximated to the nearest degree.

Savory and Moore's alumina for chromatography was used in all cases.

In the text below the phrase " in the usual way " refers to dilution with water, extraction with ether, washing successively with aqueous potassium hydroxide, aqueous hydrochloric acid, and then water, followed by evaporation of the ethereal solution *in vacuo*. Where necessary, water was removed from the residue by azeotropic distillation with benzene *in vacuo*.

Alkaline hydrolyses were effected by using several equivalents of potassium hydroxide and refluxing the reactants for 30—60 minutes in methanolic or dioxan–methanolic solution depending on the solubility of the ester.

Oxidation of Methyl Siaresinolate Acetate with Perhydrol.—Methyl siaresinolate, m. p. 175—176°, $[\alpha]_D$ +45° (*c*, 6·76), was converted into the acetate by heating it with excess of acetic anhydride in pyridine on the water-bath for 30 minutes. Recrystallised from methanol the acetate melted unsharply at 116—125°, in agreement with the findings of Bilham, Kon, and Ross (*J.*, 1942, 540).

Methyl siaresinolate acetate (1·10 g.) in 40 ml. of " AnalaR " glacial acetic acid was treated dropwise at 100° with a mixture of 10 ml. of acetic acid and 10 ml. of perhydrol during 60 minutes. Hot water

was then added until crystallisation began. Recrystallisation of the product from methanol containing a trace of chloroform gave *methyl* 19-*hydroxy*-12-*keto-oleananolate acetate* (400 mg., 36%), m. p. 230—232°, $[\alpha]_D$ +2° (c, 2·53) (Found: C, 72·8; H, 9·3. $C_{33}H_{52}O_6$ requires C, 72·75; H, 9·6%). In another experiment 730 mg. of the ketone were obtained from 2·0 g. of methyl siaresinolate acetate.

Methyl 19-*Hydroxy*-12-*keto-oleananolate*.—Hydrolysis by 10% potassium hydroxide in methanolic-dioxan of the above-mentioned acetate methyl ester afforded *methyl* 19-*hydroxy*-12-*keto-oleananolate*, which recrystallised from methanol, had m. p. 234—236°, $[\alpha]_D$ −7° (c, 1·60), giving a 20° depression in m. p. on admixture with starting material (Found: C, 73·0; H, 9·75. $C_{31}H_{50}O_4,0{\cdot}5CH_3{\cdot}OH$ requires C, 72·9; H, 10·1%). Reacetylation by acetic anhydride in pyridine regenerated starting material, m. p. and mixed m. p. 230—232°. Benzoylation of the alcohol by benzoyl chloride in pyridine at room temperature during 24 hours furnished *methyl* 19-*hydroxy*-12-*keto-oleananolate benzoate*, which, recrystallised from methanol, had m. p. 201—203° (Found: C, 75·2; H, 8·95. $C_{38}H_{54}O_6$ requires C, 75·2; H, 9·0%).

Wolff–Kishner Reduction of Methyl 19-*Hydroxy*-12-*keto-oleananolate Acetate*.—The acetate methyl ester (690 mg.) was reduced in two batches, each being heated with 350 mg. of sodium (dissolved in 4 ml. of alcohol and 2 ml. of anhydrous hydrazine) for 15 hours at 180—200°. The reaction products were combined, worked up in the usual way, methylated with diazomethane, and acetylated with excess of acetic anhydride in pyridine on the water-bath for ½ hour. Working up in the usual way and recrystallisation from aqueous methanol gave a product, m. p. 180—185°, $[\alpha]_D$ +19° (c, 3·01). This was purified by chromatography as indicated below, each fraction being crystallised once from methanol.

Fraction no.	Eluant.	M. p.
1	70 Ml. light petroleum (b. p. 40—60°)	trace, oily
2	50 Ml. 80 : 20 light petroleum (b. p. 40—60°)–benzene	trace
3	50 Ml. 75 : 25 ,, ,, ,,	218—240°
4	70 Ml. ,, ,, ,, ,,	195—198 (45 mg.)
5	70 Ml. ,, ,, ,, ,,	199—205 (30 mg.)
6	70 Ml. ,, ,, ,, ,,	208—210
7	70 Ml. ,, ,, ,, ,,	—
8	70 Ml. 50 : 50 ,, ,, ,,	209—211
9	70 Ml. ,, ,, ,, ,,	—
10	70 Ml. Benzene	201—204
11	70 Ml. ,,	—
12	70 Ml. ,,	200—203
13	120 Ml. ,,	trace
14	70 Ml. 25 : 75-ether : benzene	trace

Fractions 7 and 8 combined had $[\alpha]_D$ +18° (c, 1·19). Fractions 4—12 were combined and recrystallised from methanol, to give 420 mg. (60%) of *methyl dihydrosiaresinolate 2-acetate*, m. p. 209—211°, $[\alpha]_D$ +18° (c, 1·19) (Found: C, 75·05; H, 10·2. $C_{33}H_{54}O_5$ requires C, 74·7; H, 10·3%). Alkaline hydrolysis of this acetate methyl ester afforded *methyl dihydrosiaresinolate*, which, recrystallised from methanol, had m. p. 205—206°, $[\alpha]_D$ +10° (c, 1·35) (Found: C, 75·85; H, 10·65. $C_{31}H_{52}O_4$ requires C, 76·15; H, 10·75%).

Benzoylation of methyl dihydrosiaresinolate by benzoyl chloride in pyridine over-night furnished, after working up in the usual way, *methyl dihydrosiaresinolate 2-benzoate*, which, recrystallised from chloroform–methanol, had m. p. 225—227°, $[\alpha]_D$ +37° (c, 1·42) (Found: C, 77·45; H, 9·6. $C_{38}H_{56}O_5$ requires C, 76·95; H, 9·55%). On the first recrystallisation of the benzoate the double m. p. 135° and 203—210°, with solidification at about 160°, was observed.

Dehydration of Methyl Dihydrosiaresinolate Acetate.—Methyl dihydrosiaresinolate acetate (90 mg.) in 3 ml. of dry pyridine was treated dropwise with 0·4 ml. of freshly distilled phosphorus oxychloride. The solution was refluxed for 4 hours in an oil-bath, cooled, diluted with water, and worked up in the usual way. The crude reaction product had m. p. 210—250° and one recrystallisation from methanol gave 40 mg. of methyl morolate acetate, m. p. 258—260°, $[\alpha]_D$ +36° (c, 1·59). One further recrystallisation raised the m. p. to 262—263° and there was no depression in m. p. on admixture with authentic methyl morolate acetate (Barton and Brooks, *loc. cit.*) of the same m. p. and rotation. Alkaline hydrolysis of the acetate methyl ester afforded, after one recrystallisation from methanol, methyl morolate, m. p. 225—227°, $[\alpha]_D$ +24° (c, 0·58), undepressed in m. p. on admixture with an authentic specimen of the same m. p. and $[\alpha]_D$ +26° (Barton and Brooks, *loc. cit.*).

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Birkbeck College Research Laboratory,
21, Torrington Sq., London, W.C.1.
Imperial College of Science and Technology,
S. Kensington, London, S.W.7.

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62. *Zirconium Alkoxides.*

By D. C. Bradley and W. Wardlaw.

From the reaction between sodium ethoxide and zirconium tetrachloride in ethyl alcohol a complex sodium zirconium ethoxide has been isolated, but its composition does not accord with the formula $NaH[Zr(OEt)_4]$ reported by Meerwein and Bersin. Zirconium alkoxides have been prepared by treating solutions of zirconium tetrachloride in appropriate alcohols with anhydrous ammonia. The products are impure owing to hydrolysis which becomes very marked when secondary and tertiary alcohols are used. The cause of this hydrolysis is discussed. Ester-interchange has been successfully used for the preparation of various types of zirconium alkoxide. Tentative views are advanced to account for the interesting variation of the volatilities of zirconium alkoxides with structure of the alkyl group.

The reaction between zirconium tetrachloride and sodium ethoxide in ethyl alcohol presents some unusual features. Thus, Meerwein and Bersin (*Annalen*, 1929, **476**, 113) reported that zirconium tetraethoxide was not obtained directly owing to the formation of a complex sodium derivative to which the formula $NaH[Zr(OEt)_4]$ was assigned :

$$ZrCl_4 + 5NaOEt + EtOH = NaH[Zr(OEt)_4] + 4NaCl$$

These authors obtained zirconium tetraethoxide by the reaction :

$$NaH[Zr(OEt)_4] + HCl = Zr(OEt)_4 + NaCl + 2EtOH$$

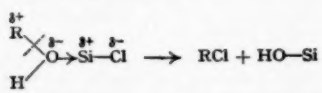
In addition, they recorded that zirconium tetraethoxide reacted with sodium ethoxide in accordance with the equation :

$$Zr(OEt)_4 + NaOEt + EtOH = NaH[Zr(OEt)_4]$$

Analogous reactions were described involving methyl alcohol in place of ethyl alcohol. We have re-investigated some of these reactions but have been unable to confirm the results of Meerwein and Bersin. However, we have found that zirconium ethoxide is readily prepared when alcohol and zirconium tetrachloride interact in the presence of ammonia. Further, this method has been successfully applied to the preparation of other zirconium alkoxides where R in the following equation is *n*-propyl, *n*-butyl, or *n*-amyl :

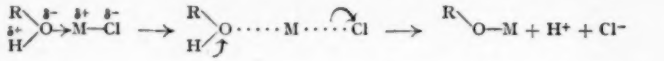
$$ZrCl_4 + 4ROH + 4NH_3 \longrightarrow Zr(OR)_4 + 4NH_4Cl$$

When secondary alcohols are used the products are appreciably hydrolysed, whilst attempts to use this method with tertiary alcohols failed. A survey of the literature disclosed that similar observations had been made in experiments designed to prepare alkoxides of silicon and titanium (Ridge and Todd, *J.*, 1949, 2637; Speer, *J. Org. Chem.*, 1949, **14**, 655). It is evident that the structure of the alcohol has a controlling influence on the degree of hydrolysis of the product resulting from the reaction of the alcohol with $SiCl_4$, $TiCl_4$, or $ZrCl_4$. Ridge and Todd (*loc. cit.*) accounted for the formation of alkyl chloride when silicon tetrachloride reacted with alcohols containing $(+I)$ alkyl groups by suggesting that the $\overset{\delta+}{R}—\overset{\delta-}{O}$ bond was broken, *i.e.* :



We believe the splitting of the R–OH bond to be less probable than the liberation of the proton from RO–H, even in the case of tertiary alcohols, and suggest an alternative explanation.

If it is assumed that the mechanism of the substitution reactions of these tetrachlorides is always of the following type (cf. Bradley, Halim, and Wardlaw, *J.*, 1950, **3451**) :



then the hydrolysis will be caused by the water liberated in the secondary reaction between hydrogen chloride and the alcohol. The experimental facts are readily explicable on this basis as it is well known that the reaction rates of alcohols with hydrogen chloride are in the order: tertiary > secondary > primary.

In addition, we find that tertiary alkoxides of both silicon and titanium have been successfully prepared from the appropriate tetrachloride and alcohol in the presence of a tertiary base which minimises the concentration of hydrogen chloride. For example, the compounds $Si(OR)Cl_3$, $Si(OR)_2Cl_2$, and $Si(OR)_3Cl$ (where R = *tert.*-butyl or *tert.*-amyl) were prepared by Miner, Bryan, Holysz, and Pedlow (*Ind. Eng. Chem.*, 1947, **39**, 1368), from appropriate amounts of pyridine, silicon tetrachloride, and tertiary alcohol:

$$SiCl_4 + 2ROH + 2C_5H_5N \longrightarrow Si(OR)_2Cl_2 + 2C_5H_5N,HCl$$

Similarly, Cullinane and Chard (*Nature*, 1949, **164**, 710) reported the preparation of titanium tetra-*tert.*-butoxide from titanium tetrachloride by a method involving the use of pyridine followed by ammonia. We are exploring the possibilities of preparing zirconium alkoxides by using bases other than ammonia.

Zirconium alkoxides exhibit the interesting property of ester interchange when treated with alcohols:

$$Zr(OR)_4 + 4R'OH \rightleftharpoons Zr(OR')_4 + 4ROH$$

This presents possibly the best general method for the preparation of pure zirconium alkoxides. Both the tetraethoxide and the tetra*iso*propoxide can be obtained pure for use as starting materials. The impure zirconium tetraethoxide, prepared by the ammonia method, can be purified by fractional crystallisation from benzene. The impure zirconium *iso*propoxide, prepared either by the direct ammonia method or from the impure ethoxide by ester interchange, is readily purified by crystallisation from *iso*propyl alcohol as the complex $Zr(OPr^i)_4.Pr^iOH$ (I). This compound was converted into other zirconium alkoxides by treatment with the following alcohols: methyl, ethyl, *n*-butyl, *sec.*-butyl, *tert.*-butyl. The range of alcohols used indicates the scope of the ester interchange reaction.

The new zirconium alkoxides show a striking variation in physical properties. It is convenient to separate them into three groups depending on whether the alkyl group is primary, secondary, or tertiary.

(1) Primary alkoxides. Zirconium tetramethoxide and tetraethoxide are white microcrystalline solids sparingly soluble in organic solvents. As the normal hydrocarbon chain is lengthened, the zirconium alkoxides change gradually from the crystalline $Zr(OEt)_4$ to the viscous liquid $Zr(OC_5H_{11}\text{-}n)_4$. These alkoxides showed little variation in volatility and sublimed between 120° and 160° under *ca.* 10^{-4} mm. pressure.

(2) Secondary alkoxides. Zirconium tetra*iso*propoxide, obtained by heating the crystalline complex (I) under reduced pressure, was a glassy solid readily soluble in organic solvents. It softened over the range 105—120° to a liquid which distilled at 160°/0·1 mm. and was clearly much more volatile than the primary alkoxides. The crystalline complex (I) melted at 138—141° and was sparingly soluble in *iso*propyl alcohol at room temperature. The tetra-*sec.*-butoxide was a gum which could be crystallised from *sec.*-butyl alcohol presumably as the addition compound $Zr(OBu^s)_4.Bu^sOH$, but the latter was very soluble in organic solvents and readily parted with its alcohol on being dried.

(3) Zirconium tetra-*tert.*-butoxide is strikingly different from any of the other alkoxides, being a colourless mobile liquid boiling at 75—76·5°/1·7 mm. and burning with a yellow flame. It was first prepared by the action of heat on the solid hydrolysed product obtained from the tetra*iso*propoxide by ester interchange. Using the boiling points obtained at two pressures we have calculated the latent heat of vaporisation of this alkoxide to be approximately 15 kcals./g.-mol. The liquid *tert.*-butoxide was readily hydrolysed on exposure to the atmosphere.

The outstanding feature of these zirconium alkoxides is the increase in volatility as the alkyl group is changed from primary to secondary to tertiary. We hope in due course, as a result of physical measurements, to be in a position to account for these properties from a structural point of view. It seems evident that either intermolecular bonding of unusual strength or a high degree of ionic character must be responsible for the low volatility of the primary alkoxides. It is also tempting to postulate that increased branching of the alkyl group sterically prevents close intermolecular bonding between zirconium and oxygen and thus leads to increased volatility. The (+*I*) inductive effect of the alkyl group may also play an

important part since increased branching gives an increased ($+I$) effect and hence a smaller degree of ionic character in the zirconium alkoxide.

The series of alkoxides of silicon, titanium, and zirconium exhibit a remarkable change in physical properties. For example, although the alkyl orthosilicates are, as expected, only slightly less volatile than their orthocarbonate analogues, yet the comparable alkoxides of titanium and zirconium show striking decreases in volatility. The following boiling-point data serve to emphasize this: $C(OEt)_4$ 158°; $Si(OEt)_4$ 165·5°; $Ti(OEt)_4$ 142°/18 mm.; $Zr(OEt)_4$ 120°/10^{-4} mm.; $C(OPr^n)_4$ 224°; $Si(OPr^n)_4$ 225—227°; $Ti(OBu^n)_4$ 135°/0·8 mm.; $Zr(OBu^n)_4$ 160°/10^{-4} mm. The boiling points of the isomeric butyl orthotitanates, reported by Speer (*loc. cit.*), reveal an influence of chain branching on volatility similar to that which we have described in the case of the zirconium alkoxides: $Ti(OBu^n)_4$ 134—136°/0·5—1·0 mm.; $Ti(OBu^i)_4$ 141°/1 mm.; $Ti(OBu^s)_4$ 90—92°/0·5—1·0 mm.; $Ti(OBu^t)_4$ 62—63°/1 mm. The effect is just perceptible in the following boiling-point data for the isomeric dibutoxydichlorosilanes: $SiCl_2(OBu^n)_2$ 94°; $SiCl_2(OBu^n)(OBu^t)$ 83°; $SiCl_2(OBu^s)(OBu^t)$ 80°; $SiCl_2(OBu^t)_2$ 70°, all at 15 mm. pressure (calculated from data given by H. W. Post in "Organic Silicon Compounds," Reinhold, 1949).

The important features which emerge from this preliminary survey are: (i) that the increases in boiling points of alkoxides containing a given *n*-alkyl group, when the central atom changes from silicon to titanium to zirconium, are much greater than is expected on the simple basis of increases in molecular weight; (ii) that the increase in volatility resulting from branching of the alkyl groups, in isomeric alkoxides, is common to the alkoxides of these elements but the magnitudes of this effect are in the order, Zr > Ti > Si. These points suggest that striking differences can be expected in either the degree of molecular complexity or the amount of ionic character in the orthoesters (alkoxides) of silicon, titanium, and zirconium.

Experimental.

Special precautions were taken to exclude moisture and all-glass apparatus was used.

Chemicals.—Zirconium tetrachloride was a pale yellow powder (Found: Zr, 39·0. Calc. for $ZrCl_4$: Zr, 39·1%).

Methyl and ethyl alcohols were dried over the respective magnesium alkoxide and then fractionally distilled. Other alcohols were dried over the appropriate aluminium alkoxide and fractionally distilled.

Benzene (AnalaR) was dried over sodium wire and distilled.

Analytical Methods.—Zirconium and chloride were determined gravimetrically as zirconium oxide and silver chloride respectively.

Sodium was determined, after removal of zirconium, by evaporating the filtrate to dryness and converting the residue into either sodium chloride or sodium sulphate.

The oxidation method, described previously (Bradley, Halim, and Wardlaw, *loc. cit.*), was used for ethoxide and *iso*propoxide determinations.

The same reagent was used for determining methoxide or *sec.*-butoxide, but the method was modified as follows:

(i) Methoxide. The reactants, after being kept for 2 hours at room temperature, were heated until effervescence ceased and the formation of carbon dioxide was thus complete.

(ii) *sec.*-Butoxide. The reactants were kept for 1 hour. Trial experiments on pure substances indicated that high results were otherwise obtained.

Analyses for carbon and hydrogen were carried out by Messrs. Weiler and Strauss, Oxford.

(a) *Reactions between Sodium Ethoxide and Zirconium Tetrachloride.*—The conditions recorded by Meerwein and Bersin (*loc. cit.*) were closely followed. Zirconium tetrachloride (10 g., 1 mol.) was dissolved in ethyl alcohol (35 c.c.) and to this solution sodium ethoxide solution [4·3 g. (4·5 atoms) of sodium in 75 c.c. of alcohol] was slowly added, a finely divided precipitate being formed. After filtration, more sodium ethoxide (0·5 g. of sodium in 10 c.c. of ethanol) was added to the solution which was set aside for 24 hours. The crystalline product was washed with alcohol and one portion dried over sulphuric acid (d 1·84) in an evacuated desiccator (Found: Zr, 31·7; Na, 5·4%; Zr/Na, 1·48). The remainder of the product was recrystallised from xylene and dried under 0·5 mm. pressure {Found: Zr, 32·2; Na, 5·3; C, 31·1; H, 6·8; Zr/Na, 1·52; Cl, trace. Calc. for $NaH[Zr(OEt)_4]$: Zr, 23·6; Na, 6·0; C, 37·4; H, 8·1%}. A second crop of crystals, obtained from the alcoholic mother-liquor, was recrystallised from xylene, and the final product dried over silica gel at atmospheric pressure (Found: Zr, 32·1; Na, 5·4; C, 30·7; H, 6·8%; Zr/Na, 1·50).

In another experiment, a solution of sodium (6·4 g.) in ethanol (110 c.c.) was added to the cooled (10°) solution of zirconium tetrachloride (14·5 g.) in alcohol (54 c.c.). The reactants were heated to boiling and filtered. Addition of sodium ethoxide to the filtrate did not cause crystallisation but the original precipitate was heavily contaminated with zirconium. This precipitate was extracted with alcohol (300 c.c.) and filtered at the boiling point. The filtrate was concentrated to 100 c.c. and furnished some solid (5 g.) which was recrystallised from toluene (100 c.c.). The colourless hexagonal prisms were

dried over silica gel [Found: Zr, 32·0; Na, 5·4; EtO, 55·0; Zr/Na, 1·50; EtO/Zr, 3·48. $Zr_8Na_4(OEt)_{31}(OH)_7$ requires Zr, 32·1; Na, 5·4; EtO, 55·5%].

These experiments showed that the complex *sodium* salt readily co-precipitated with the sodium chloride. The method of preparation was modified as follows: Ethyl alcohol (150 c.c.) was added to zirconium tetrachloride (18·6 g.) and the solution analysed for chloride. Enough sodium ethoxide, just to combine with this chloride, was then added. Thus, sodium ethoxide (6·15 g. of sodium in 100 c.c of ethanol) was slowly added to the zirconium tetrachloride solution. After 10 minutes' boiling, the mixture was filtered and more sodium ethoxide (sodium, 1·2 g.; ethanol, 50 c.c.) added to the filtrate which was set aside for 2 days. The precipitated sodium chloride was again contaminated with zirconium. The filtrate deposited a crystalline mass which was recrystallised from toluene, and the final product (7·7 g.) was dried under 0·1 mm. pressure at room temperature (Found: Zr, 31·7; Na, 5·3%; Zr/Na, 1·50). The alcoholic mother-liquor yielded more solid which, after recrystallising from toluene, weighed 2·5 g. and raised the overall yield of sodium zirconium ethoxide to 45%. This experiment established that during the addition of sodium ethoxide to an alcoholic solution of zirconium tetrachloride only part of the sodium combined with the chloride, and the rest was associated with zirconium.

(b) *Preparation of Zirconium Alkoxides by the Ammonia Method.*—For primary alkoxides the same general procedure was used throughout.

Zirconium tetraethoxide. Ammonia was passed into a solution of zirconium tetrachloride (52·5 g.) in ethyl alcohol (200 c.c.), giving a voluminous precipitate. The reaction is exothermic and the treatment with ammonia was continued until the solution had cooled to room temperature. Free ammonia was then removed under reduced pressure and the products were filtered off. After being washed with alcohol (50 c.c.), the residue (54 g.) had a zirconium content equivalent to 2·6% of ZrO_2. The clear filtrate was concentrated under reduced pressure and gave more ammonium chloride (the solubility of ammonium chloride in alcohols was increased in the presence of ammonia). The final filtrate was evaporated to dryness at 1 mm. and the pale yellow solid (47·3 g.) dried at 60° [Found: Zr, 35·2; EtO, 63·4; Cl, 0·25; EtO/Zr, 3·65. $Zr(OEt)_4$ requires Zr, 33·6; EtO, 66·4%]. The impure zirconium ethoxide was very soluble in benzene, carbon tetrachloride, or light petroleum. The pure *ethoxide* was obtained as follows: Impure zirconium ethoxide (13 g.) was dissolved in boiling benzene (130 c.c.) and allowed to crystallise. The finely divided crystals were separated, by means of a filter stick, from the yellow mother-liquors and recrystallised five times. The zirconium tetraethoxide (8·4 g.) thus obtained was a white microcrystalline solid (Found: Zr, 33·9; EtO, 65·9%). The pure compound was moderately soluble in boiling benzene but only sparingly soluble in hot ethyl alcohol. When heated in a " molecular still " it sublimed at 120° under 10^{-4} mm. pressure. The substance melted at 171—173° after exhibiting a transient phase change above 120° (depending on the rate of heating).

When sodium ethoxide was titrated against solutions of zirconium tetraethoxide in benzene–alcohol, sharp end-points (to thymolphthalein) were obtained after the addition of 0·5 equiv. of NaOEt per mol. of $Zr(OEt)_4$ [0·9286 g. and 0·5175 g. of $Zr(OEt)_4$ required 14·99 and 8·04 c.c. respectively of 0·111N-NaOEt. Calc. for ½ equiv. of NaOEt: 15·38 and 8·55 c.c.]. According to Meerwein and Bersin (*loc. cit.*) zirconium ethoxide (1 mol.) required 1 equiv. of NaOEt, yet the analytical formula of our sodium zirconium ethoxide suggests that 2/3 equiv. should be required. This problem is still under investigation.

Zirconium n-*propoxide.* Zirconium tetrachloride (5·5 g.) was dissolved in *n*-propyl alcohol (120 c.c.) and the solution treated with ammonia. After removal of the ammonium chloride and solvent, an impure zirconium *n*-propoxide was obtained as a dark brown solid (4·9 g.) [Found: Zr, 31·0. Calc. for $Zr(OC_3H_7)_4$: Zr, 27·8%]. This compound could not be crystallised from benzene or carbon tetrachloride neither could it be sublimed even at 150°/10^{-4} mm.

Zirconium n-butoxide. The impure zirconium *n*-butoxide, isolated from the reaction of ammonia with the solution of zirconium tetrachloride (9·2 g.) in *n*-butyl alcohol (100 c.c.), was a brown gummy solid [Found: Zr, 25·8. Calc. for $Zr(OC_4H_9)_4$: Zr, 23·8%]. The product was soluble in benzene but could not be crystallised. When heated at 160°/10^{-4} mm. the product gave a translucent gummy sublimate (Found: Zr, 25·2%).

Zirconium n-*amyloxide.* Zirconium tetrachloride (9·2 g.) in *n*-amyl alcohol (100 c.c.) was treated with ammonia, and the impure zirconium alkoxide obtained as a clear, golden viscous liquid (15·3 g.) [Found: Zr, 21·7. Calc. for $Zr(OC_5H_{11})_4$: Zr, 20·7%]. The product was volatile at 160°/10^{-4} mm. and gave a viscous condensate which contained zirconium and liberated amyl alcohol when hydrolysed.

Zirconium iso*propoxide.* In preliminary experiments, two difficulties were encountered in the preparation of zirconium *iso*propoxide: (i) the complex *iso*propoxide $Zr(OPr^i)_4.Pr^iOH$, being sparingly soluble in *iso*propyl alcohol, was co-precipitated with the ammonium chloride and (ii) a considerably hydrolysed *iso*propoxide was obtained. The following procedure was evolved to minimise these disadvantages:

Zirconium tetrachloride (19·8 g.) was slowly added to *iso*propyl alcohol (125 c.c.) saturated with ammonia at 5°. After 2 hours' refluxing the products were filtered off at the boiling point. The residue (16·4 g.; theory for NH_4Cl, 18·0 g.), after extraction with hot benzene (75 c.c.), contained only a trace of zirconium. The filtrate and extracts were combined and concentrated to remove most of the *iso*propyl alcohol. More benzene (100 c.c.) was added and the solution treated with ammonia for 2 hours. The additional precipitate was removed and the filtrate evaporated to dryness at 80° under reduced pressure. The gummy solid (21·0 g.) was analysed with difficulty [Found: Zr, 31·6; C_3H_7O, 63·1; C_3H_7O/Zr, 3·09. Calc. for $Zr(OC_3H_7)_4$: Zr, 27·8; C_3H_7O, 72·2%].

The impure zirconium *iso*propoxide (19·8 g.) dissolved in boiling *iso*propyl alcohol (200 c.c.), and a mass of colourless crystals separated on cooling. The crystalline *complex* (17·2 g.) was dried at room

temperature/0·5 mm. [Found: Zr, 24·1; C_3H_7O, 75·4; $Zr(OC_3H_7)_4.C_3H_7{\cdot}OH$ requires Zr, 23·5; C_3H_7O, 76·2%]. This crystallisation clearly affords a ready means of purifying the crude *iso*propoxide.

Zirconium sec.-*butoxide*. Treatment of zirconium tetrachloride (18·6 g.) in *sec.*-butyl alcohol (100 c.c.) with ammonia gave, after removal of ammonium chloride and solvent, a gummy product (19·4 g.) which was evidently considerably hydrolysed [Found: Zr, 31·9; C_4H_9O, 63·1. Calc. for $Zr(OC_4H_9)_4$: Zr, 23·8; C_4H_9O, 76·2%].

Zirconium tert.-*butoxide*. Zirconium tetrachloride, added to ammoniacal ether–*tert.*-butyl alcohol and treated for a long time with ammonia, gave a hydrolysed zirconium alkoxide which still contained chloride reactive to sodium *tert.*-butoxide. Zirconium *tert.*-butoxide was then prepared as follows:

To a solution of sodium (10·2 g.) in *tert.*-butyl alcohol (450 c.c.), zirconium tetrachloride (25·8 g.) was carefully added and the products were refluxed for 8 hours. The suspension was centrifuged and the clear mother-liquor evaporated to dryness under reduced pressure. The solid product melted at *ca.* 230° under 1 mm. pressure and a volatile liquid (5·8 g.) was collected as the bath-temperature rose to 260°. This liquid *tetra*-tert.-*butoxide* was redistilled at 75—76·5°/1·7 mm. pressure and gave a colourless mobile distillate (2·4 g.) [Found: Zr, 23·35. $Zr(OC_4H_9)_4$ requires Zr, 23·8%].

(c) *Ester-interchange Experiments.*—Because of the reversibility of ester-interchange reactions, the required alkoxide was obtained by employing a large excess of the reacting alcohol and fractionating the mixture to remove the more volatile liberated alcohol. The course of the reaction was followed by refractive-index and boiling-point measurements on the distillate. A 50-cm. column, packed with Fenske helices, was used in conjunction with a Whitmore–Lux-pattern total-condensation variable-take-off stillhead. When the liberated alcohol was less volatile than the reacting alcohol a different procedure was followed.

Preparation of zirconium iso*propoxide from zirconium ethoxide*. Impure zirconium ethoxide (20·7 g.) was refluxed with *iso*propyl alcohol (600 c.c.) at 130° for several days during which the alcohols were fractionated at a high reflux ratio. After collection of 500 c.c. of distillate, the crystals which deposited on cooling of the mixture were separated from the yellow mother-liquor. More *iso*propyl alcohol (600 c.c.) was added to the crystals and the fractionation continued. 300 c.c. of distillate were collected and the remaining solution was allowed to cool. The crystalline complex (30·2 g.) was washed twice and dried at room temperature under 1 mm. pressure (Found: Zr, 23·9; C_3H_7O, 75·8%). An active-hydrogen determination confirmed the presence of 1 mol. of *iso*propyl alcohol per atom of zirconium in the complex [Found: 0·7722 g. of compound liberated 48·2 c.c. (at N.T.P.) of gas. $Zr(OC_3H_7)_4.C_3H_7{\cdot}OH$ requires 44·5 c.c.]. The compound melted (capillary tube) at 138—141° and decomposed (loss of *iso*-propyl alcohol) above 144°. When the crystalline compound (5·3 g.) was heated at 90—120°/1 mm. it melted and effervesced, leaving a liquid which set to a glassy translucent solid (4·5 g.) on cooling. *iso*Propyl alcohol was collected in the cold trap. The zirconium tetra*iso*propoxide prepared in this way was distilled at 160°/0·1 mm. A water-white viscous liquid was collected which set to a glassy solid (3·7 g.). This solid *zirconium tetraisopropoxide* melted over the range 105—120° [Found: Zr, 28·3; C_3H_7O, 71·15. $Zr(OC_3H_7)_4$ requires Zr, 27·8; C_3H_7O, 72·2%].

Preparation of zirconium methoxide from zirconium iso*propoxide*. Methyl alcohol (200 c.c.) was added to zirconium tetra*iso*propoxide (4·5 g.) and refluxed for 7 hours at 75°. The zirconium *iso*propoxide did not appear to dissolve but disintegrated to a fine white powder. The mixture of alcohols was evaporated under reduced pressure at 0° and the resulting white powder treated with more methyl alcohol (200 c.c.) and refluxed for 8 hours. The solid remaining after removal of the alcohols was dried at room temperature under 1 mm. pressure [Found: Zr, 43·1; MeO, 55·7; C, 21·4; H, 5·2. $Zr(OMe)_4$ requires Zr, 42·4; MeO, 57·6; C, 22·3; H, 5·6%]. The *zirconium tetramethoxide* appeared to be insoluble in methyl alcohol or benzene even at the boiling point.

Reaction of ethyl alcohol with zirconium iso*propoxide*. Ethyl alcohol (180 c.c.) was added to the complex $Zr(OPr^i)_4.Pr^iOH$ (4·6 g.) and refluxed for 12 hours. The mixture of alcohols was distilled under 1 mm. pressure at room temperature, giving impure tetraethoxide [Found: Zr, 33·3; EtO, 63·6. Calc. for $Zr(OEt)_4$: Zr, 33·6; EtO, 66·4%]. The analysis suggested that ester-interchange was not complete but the experiment confirmed the reversibility of the system:

$$Zr(OEt)_4 + 5Pr^iOH \rightleftharpoons Zr(OPr^i)_4.Pr^iOH + 4EtOH$$

Preparation of zirconium n-*butoxide from zirconium* iso*propoxide*. *n*-Butyl alcohol (100 c.c.) was added to the complex, $Zr(OPr^i)_4.Pr^iOH$ (6·4 g.) and slowly fractionated. The distillate (85 c.c.) was estimated to contain 5·7 c.c. of *iso*propyl alcohol (theor., 6·0 c.c.). The remaining solvent was distilled off under reduced pressure leaving the *tetra*-n-*butoxide* as a glassy solid [Found: Zr, 24·0. $Zr(OC_4H_9)_4$ requires Zr, 23·8%]. The product melted over the range 65—75°.

Preparation of zirconium sec.-*butoxide from zirconium* iso*propoxide*. *sec.*-Butyl alcohol (110 c.c.) was added to the *iso*propoxide complex (5·05 g.) and slowly fractionated. The reaction was estimated to be complete when 75 c.c. of distillate had been collected and the remainder of the solvent was then distilled off under reduced pressure. The gummy product was dried at 110°/0·5 mm. [Found: Zr, 25·3; C_4H_9O, 74·8. Calc. for $Zr(OC_4H_9)_4$: Zr, 23·8; C_4H_9O, 76·2%]. The zirconium tetra-*sec.*-butoxide was crystallised from *sec.*-butyl alcohol, but although the crystalline product was dried at room temperature under 1 mm. pressure it is suspected that partial loss of alcohol of crystallisation occurred [Found: Zr, 22·8; C_4H_9O, 79·8. Calc. for $Zr(OC_4H_9)_4.C_4H_9{\cdot}OH$: Zr, 19·9; C_4H_9O, 79·9%]. This compound melted at 60—70° under 0·5 mm. pressure, and at 80° was clearly losing alcohol of crystallisation.

Preparation of zirconium tert.-*butoxide from zirconium* iso*propoxide*. *tert.*-Butyl alcohol (350 c.c.) was refluxed for 12 hours with the *iso*propoxide complex (4·3 g.) and then fractionated for 23 hours. The distillate (75 c.c.) contained 2·6 g. of *iso*propyl alcohol (theor., 2·65 g.). After filtration,

the solution was evaporated to dryness under reduced pressure and gave a gummy product (3 g.) (Found : Zr, 26·65%). This substance melted at 100° under 0·2 mm. pressure to a volatile liquid which distilled at 45·5—46·5° although the bath-temperature rose to 135° [Found : Zr, 22·8; C, 45·9; H, 8·8. Calc. for $Zr(OC_4H_9)_4$: Zr, 23·8; C, 50·1; H, 9·5%]. This liquid burned readily with a yellow flame, leaving a deposit of zirconium oxide. By applying the Clausius–Clapeyron equation to the temperature–vapour pressure data (1·7 mm. at 76°; 0·2 mm. at 46°) the approximate value of 15 kcals./g.-mol. was found for the latent heat of vaporisation of zirconium tetra-*tert.*-butoxide.

Reaction between Zirconium Tetrachloride and tert.*-Butyl Alcohol.—tert.*-Butyl alcohol (35 c.c.) was added to zirconium tetrachloride (8·8 g.). A sluggish reaction occurred with precipitation of zirconium hydroxide. After 10 minutes' refluxing, the product was distilled and *ca.* 25 g. of distillate (b.r. 40—80°) were collected. This liquid was washed with water and dried over potassium carbonate, and furnished a fraction (8·4 g.) which boiled at 45—53° (cf. *tert.*-butyl chloride, b. p. 51—52°). Thus, about 60% of the available chloride in zirconium tetrachloride was recovered as *tert.*-butyl chloride.

BIRKBECK COLLEGE, LONDON, E.C.4. [*Received, October 7th,* 1950.

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63. *Synthesis of Trehalose-type Disaccharides.*

By VIOLET E. SHARP and M. STACEY.

Fusion of acetohalogeno-sugars in air with molten sodium leads to the production of non-reducing disaccharides of the trehalose type. These have been synthesised by alternative methods, and the constituent monosaccharides appear to have α β-configuration.

FOLLOWING the methods described previously (Gilbert, Stacey, and Smith, *J.*, 1946, 622) for the direct constitutional synthesis of cellobiose and gentiobiose, we have made numerous unsuccessful attempts to synthesise octa-acetyl maltose by the condensation of 4-sodio-D-glucopyranose 1 : 2 : 3 : 6-tetra-acetate and β-acetofluoro-D-glucopyranose. There appeared to be much deacetylation and acyl migration, and there was no evidence that any significant amount of disaccharide, other than traces of non-reducing products, had been synthesised. Similar attempts to synthesise directly a lactose derivative by condensing α-acetobromogalactose with 4-sodio-D-glucopyranose 1 : 2 : 3 : 6-tetra-acetate were unsuccessful. In this reaction, however, there was produced an appreciable amount of disaccharide material which, after separation on an alumina column, was obtained crystalline. This was a non-reducing disaccharide derivative which was shown to be an octa-acetyl galactobiose and it evidently resulted from the action of sodium on the α-acetobromogalactose. It is well known that trehalose-type disaccharides have been made before in condensation reactions, as for example in the attempted synthesis of sucrose (for references, see Pigman and Goepp, " Chemistry of the Carbohydrates," Academic Press, 1948, p. 451). We decided to investigate the action of sodium on acetohalogeno-sugars. In one example α-acetobromogalactose in the liquid state was heated with sodium in the presence of essentially oxygen-free nitrogen and even after several hours of heating there was no reaction, the sodium globules remaining bright and unchanged. However, in a similar reaction in air, the sodium dissolved gradually and there was a slow separation of sodium bromide. The product of this reaction, obtained in about 50% yield, was an octa-acetyl disaccharide which did not reduce Fehling's solution. Deacetylation produced a crystalline non-reducing disaccharide which yielded only D-galactose on acid hydrolysis. This was apparently identical with Vogel and Debowska-Kurnicka's galactobiose (*Helv. Chim. Acta*, 1928, **11**, 910), which was shown by them to be α-D-galactopyranosyl-β-D-galactopyranoside. Their product was made by the action of phosphoric oxide in dry chloroform on β-D-galactose 2 : 3 : 4 : 6-tetra-acetate. In our disaccharide, the presence of the glycosidic link was shown by the ease of acid hydrolysis of the galactobiose to form galactose, and it was of interest to find that this type of ether linkage and not a C–C linkage had been formed by the action of the sodium on the glycosyl bromide. No condensation could be achieved by the action of dry sodium hydroxide on the glycosyl bromide, and sodium oxide was probably the effective condensing agent.

The non-reducing disaccharide produced during the attempted synthesis of maltose mentioned above could also be obtained in small yield by the action of sodium in air on β-acetofluoro-D-glucose alone. A much more convenient synthesis of the same compound was, however, achieved by the action on β-acetofluoroglucose of the reagents described by McCloskey, Pyle, and Coleman (*J. Amer. Chem. Soc.*, 1944, **61**, 349) for the synthesis of gentiobiose, etc. The method consisted in shaking the acetofluoroglucose for 48 hours in the dark with a mixture of

silver carbonate, anhydrous magnesium perchlorate, and iodine, followed by chromatographic separation of the products on a silica gel column. The separation of the disaccharide component was controlled by the determination of the molecular weight of the separated crystalline fractions. For this determination the method normally used was that of Rast, employing as solvent either camphor or the less well-known but very useful solvent, the lactam of *cis*-p-aminohexahydrobenzoic acid (Wendt, *Ber.*, 1942, **75**, 425). After purification, the non-reducing disaccharide acetate was identified, as described in the Experimental section, as the octa-acetyl derivative of α-D-glucopyranosyl-β-D-glucopyranoside (αβ-trehalose) which was smoothly converted into the crystalline sugar, αβ-trehalose. Theoretically there are three non-reducing trehalose-type disaccharides for each dihexose. For example, with a diglucose type linked through the reducing positions there could be the αα-, the αβ-, and the ββ-trehalose.

The naturally-occurring non-reducing disaccharide trehalose, isolated from ergot or from young mushrooms (for references, see Harding, *Sugar*, 1923, **25**, 476), has been identified as α-D-glucopyranosyl-α-D-glucopyranoside (αα-trehalose) (Schlubach and Maurer, *Ber.*, 1925, **58**, 1179) but it has not yet been synthesised.

Several syntheses of the ββ-trehalose from α-acetobromo-D-glucose and/or D-glucose 2 : 3 : 4 : 6-tetra-acetate have been claimed (Fischer and Delbruch, *Ber.*, 1909, **42**, 2776; Schlubach and Schetelig, *Ber.*, 1925, **58**, 1178; McCloskey, Pyle, and Coleman, *loc. cit.*). Derivatives of αβ-trehalose have previously been synthesised from β-D-glucose 2 : 3 : 4 : 6-tetra-acetate, *e.g.*, (*a*) by condensing two molecules by means of phosphoric oxide and zinc chloride (Vogel and Debowska-Kurnicka, *loc. cit.*), (*b*) by fusion with zinc chloride (Schlubach and Maurer, *loc. cit.*), and (*c*) by heating it with 1 : 2-anhydro-D-glucose 3 : 4 : 6-triacetate in benzene (Haworth and Hickinbottom, *J.*, 1931, 2947). The melting point and rotations of these derivatives have been variously quoted as shown in the table.

Compound.	M. p.	$[\alpha]_D$.	Reference.
αα-Trehalose octa-acetate	100—102°	+162·3° in chloroform	Hudson and Johnson, *J. Amer. Chem. Soc.*, 1915, **37**, 2748.
ββ-Trehalose octa-acetate	181	−18·6° in chloroform	Schlubach and Schetelig, *Z. physiol. Chem.*, 1932, **213**, 83.
αβ-Trehalose octa-acetate	68—70	+68·1 in chloroform	Vogel and Debowska-Kurnicka, *loc. cit.*
αβ-Trehalose (*neo*trehalose) octa-acetate	140—141	+82° in chloroform	Haworth and Hickinbottom, *loc. cit.*
αα-Trehalose,$2H_2O$	97	+178° in water	Schukoff, *Z. deutsch. Zuckerindustrie*, 1900, **2**, 818.
αα-Trehalose, anhydrous	203	+197° in water	Lippmann, *Ber.*, 1921, **54**, 3431.
ββ-Trehalose	130—135	−41·5° in water	Schlubach and Schetelig, *loc. cit.*
αβ-Trehalose	85	+67·1° in water	Vogel and Debowska-Kurnicka, *loc. cit.*
αβ-Trehalose (*neo*trehalose) *ca.*	145	+95° in water	Haworth and Hickinbottom, *loc. cit.*

The non-reducing disaccharide obtained in low yield by Haworth and Hickinbottom (*loc. cit.*) was termed *neo*trehalose and the authors pointed out that it differed markedly in its properties from the αβ-trehalose of Vogel and Debowska-Kurnicka (*loc. cit.*), the specific rotation of which did, however, approximate very closely that calculated ($[\alpha]_D$ +70°) by Hudson's statistical rules (*J. Amer. Chem. Soc.*, 1916, **38**, 1571). The rotations of our products prepared above appeared to resemble more closely those recorded by Vogel and Debowska-Kurnicka. In this connection it should be pointed out that recent investigations on syntheses involving the opening of ethylene oxide rings reveals that two products can be formed, so that it is theoretically possible that in addition to the *neo*trehalose, which is a " glucose 1 : 1-glucose " disaccharide, Haworth and Hickinbottom's method could also give rise to a " glucose 1 : 2-hexose " disaccharide, though this would of course have been strongly reducing.

In our synthesis of αβ-trehalose outlined above, it should be noted that on combination of the two substituted glucose molecules, Walden inversion occurred on only one of the $C_{(1)}$ atoms, whereas in Fischer and Delbruch's synthesis (*loc. cit.*) inversion must have occurred on both $C_{(1)}$ atoms. Inspection of the literature and our experiences provide insufficient evidence to indicate the precise conditions under which trehalose-type syntheses are accompanied by Walden inversion on either or both of the reacting $C_{(1)}$ atoms.

Experimental.

(Ligroin and light petroleum refer to materials of b. p. 40—60° and 60—80°, respectively.)

α-*Acetobromogalactose.*—This was prepared by the method of Ohle, Maracek, and Bourjeau (*Ber.*, 1929, **62**, 848); the water-insoluble mass solidified on being stirred with ligroin. After recrystallisation from ether–ligroin the compound had m. p. 83°.

Synthesis of Galactobiose Octa-acetate.—Dry α-acetobromogalactose (1·5 g.) was fused in an oil-bath at 90°, in a dry test-tube open to the air; sodium (0·09 g.) was added gradually with stirring and pressing with a glass rod, and the mixture was then heated at 100—110° for 4 hours, during which the sodium dissolved. After acetylation of the reaction mixture for 45 minutes at 100° with sodium acetate and acetic anhydride, the product was left overnight under ice-water. The resulting insoluble syrup was dissolved in ether, and some discoloured material was precipitated by addition of light petroleum. The filtered solution was concentrated to a syrup which was again acetylated, poured into water, and extracted by chloroform. The dried extract was evaporated to a syrup which solidified and then was crystallised from acetone by addition of ligroin (yield 0·7 g., approx. 50%).

The acetate was very soluble in chloroform and acetone, less soluble in methanol, ethanol, or ether, almost insoluble in water or light petroleum. It had m. p. 85°, $[\alpha]_D^{20}$ +58° (*c*, 1·0 in chloroform) (Found: C, 49·2; H, 5·6; OAc, 50·0. Calc. for $C_{28}H_{38}O_{19}$: C, 49·6; H, 5·6; OAc, 50·7%). [The galactobiose octa-acetate of Vogel and Debowska-Kurnicka (*loc. cit.*) had m. p. 82—83°, $[\alpha]_D$ +51·7° (*c*, 2·1 in chloroform)]. Molecular weight (Rast) in the lactam of *cis-p*-aminohexahydrobenzoic acid (Wendt, *loc. cit.*) = 680; molecular weight of a disaccharide octa-acetate = 678.

The octa-acetate was non-reducing to Fehling's solution, but yielded a strongly reducing solution after being hydrolysed for 7 hours at 85—90° with 0·6% hydrochloric acid in 1 : 1 acetone–water. A sample of the octa-acetate (30 mg.) was directly oxidised for 1 hour at 95° with 1 : 3 concentrated nitric acid–water and yielded insoluble crystals (10 mg.) of galactosaccharic acid (mucic acid), m. p. and mixed m. p. 210° (decomp.).

Galactobiose.—(a) *Preparation and properties.* Deacetylation of the octa-acetate (0·25 g.) with sodium methoxide (Zemplén, *Ber.*, 1926, **59**, 1258) yielded a crystalline disaccharide (0·1 g.), m. p. 110° (decomp.), $[\alpha]_D^{20}$ +56° (*c*, 0·4 in water) {Vogel and Debowska-Kurnicka, *loc. cit.*, give m. p. 122°, $[\alpha]_D$ +67·8° (*c*, 0·99 in water), for αβ-galactobiose}. The disaccharide was water-soluble, and non-reducing to Fehling's solution. Its reduction value was equivalent to 0·8% of glucose (Schaffer and Hartmann, *J. Biol. Chem.*, 1920, **45**, 365). After being boiled for 5 minutes with 5% hydrochloric acid, and neutralised, the solution was strongly reducing to Fehling's solution and could readily be oxidised to give galactosaccharic acid.

(b) *Hydrolysis and osazone formation.* A sample of the disaccharide (0·05 g.) was boiled for 30 minutes with 5% hydrochloric acid (5 c.c.), and concentrated in a vacuum at 60°, with removal of most of the hydrogen chloride by distillation with several additions of water, and removal of water by distillation with alcohol. The solid residue was heated for 30 minutes at 100° with water (1 c.c.), phenylhydrazine (0·1 c.c.), and glacial acetic acid (0·15 c.c.). Yellow crystals (0·02 g.) were obtained, having m. p. 188°, alone or in admixture with authentic galactosazone (m. p. 188°).

Fusion in Nitrogen.—α-Acetobromogalactose (0·5 g.) was fused at 100—110° with sodium (0·03 g.) in an atmosphere of pure dry nitrogen, for 4½ hours, after which metallic sodium was still present. The mixture was poured off the sodium, acetylated, poured into water, and extracted with chloroform, and the extract concentrated under reduced pressure (60°) to a dry syrup. When stirred with ether, this yielded crystals (0·13 g.), m. p. 138°, alone or in admixture with β-galactose penta-acetate, m. p. 140°. The solution was evaporated to a syrup having *M*, 340 (Rast camphor method). No disaccharide octa-acetate could be isolated from the products of this reaction.

Sodium Hydroxide Fusion.—α-Acetobromogalactose (0·8 g.) and solid sodium hydroxide (0·08 g.) were fused in the presence of air at 110° for 3 hours, considerable darkening occurring. After acetylation, pouring into water and extraction with chloroform, the extract was concentrated under reduced pressure (60°) to a syrup. Addition of ether gave β-galactose penta-acetate (0·25 g.), m. p. 139° alone and when mixed with an authentic specimen having m. p. 140°. The solution was evaporated to a syrup having *M*, 400. Hence this experiment also yielded no disaccharide acetate.

Attempted Synthesis of Lactose Octa-acetate.—β-D-Glucose 1 : 2 : 3 : 6-tetra-acetate (3·0 g.) (Helferich and Müller, *Ber.*, 1930, **63**, 2142) and sodium (0·16 g.) were fused in the presence of air, at 120—140° for one hour; α-acetobromogalactose (3·0 g.) was added and the mixture heated to 100° for 1½ hours and then acetylated with sodium acetate and acetic anhydride. An elaborate systematic chromatographic fractionation of the mixture on a silica column (Gilbert, Smith, and Stacey, *loc. cit.*) yielded no lactose octa-acetate but a sample (1·3 g.) of a non-reducing disaccharide octa-acetate, m. p. 83°, $[\alpha]_D^{20}$ +59° (*c*, 1·0 in chloroform), identical with the αβ-galactobiose octa-acetate described above. It was deacetylated to yield α-galactopyranosyl-β-galactoside, m. p. 110°, $[\alpha]_D^{20}$ +56° (*c*, 1·0 in water).

β-Acetofluoroglucose.—This compound was prepared from α-acetobromoglucose by the method of Helferich and Goatz (*Ber.*, 1929, **62**, 2505); it had m. p. 86°, $[\alpha]_D^{18}$ +21° (*c*, 1·2 in chloroform); combined bromine was absent, combined fluorine (cerous nitrate test) present. The compound was stable for several weeks in solution in dry ether at 0° or when kept in a vacuum over phoshoric oxide.

αβ-Trehalose Octa-acetate.—Method (A). The action of sodium on molten β-acetofluoroglucose gave non-reducing crystalline products of molecular weight of the order of 600, but the method was not persevered with since the following reaction was successful.

The general technique was similar to that of McCloskey, Pyle, and Coleman (*loc. cit.*). Solid reagents, except "Anhydrone," were dried under reduced pressure over phosphoric oxide; chloroform was five times distilled over phosphoric oxide.

β-Acetofluoroglucose (5·0 g.), silver carbonate (5·0 g.), "Anhydrone" (5·0 g.), and iodine (1·0 g.) were shaken together in the dark in chloroform (30 c.c.) for 48 hours. The solution was filtered, the residue washed with hot chloroform, and the solution freed from iodine by washing it with dilute aqueous sodium thiosulphate. The dried chloroform solution was evaporated to a syrup which was acetylated with sodium acetate and acetic anhydride at 110° for one hour, then poured into water, and extracted with

chloroform. The chloroform solution was washed with aqueous sodium hydrogen carbonate, dried, and evaporated to a glassy syrup (3·9 g.) which was twice chromatographed on silica (4 × 25 cm.) by the method of Gilbert, Smith, and Stacey (*loc. cit.*). The various fractions had molecular weights (Rast camphor method) corresponding to mixtures of monosaccharide and disaccharide acetates and hardly any separation was achieved. The bulked product was then chromatographed on B.D.H. adsorption alumina (4 × 25 cm.), yielding fractions (1*a*) 0·88 g., *M*, 560, (1*b*) 0·22 g., *M*, 680, and (1*c*) 0·02 g., *M*, 520. Fractions (1*a*) and (1*c*) were bulked and again chromatographed on alumina, yielding fractions (2*a*) 0·27 g., *M*, 510, (2*b*) 0·19 g., *M*, 700, (2*c*) 0·23 g., *M*, 700, (2*d*) 0·14 g., *M*, 660, and (2*e*) 0·07 g., *M*, 480.

Fractions (1*b*), (2*b*), (2*c*), and (2*d*) had molecular weights approximately corresponding to a fully acetylated hexose disaccharide (678) and were combined (0·78 g.; yield approx. 40%) and recrystallised several times from ether–ligroin.

The acetate, which did not reduce Fehling's solution until after acid hydrolysis, had m. p. 120°, $[\alpha]_D$ +67° (*c*, 1·0 in chloroform) (Found: C, 49·6; H, 5·6%; *M*, 690. Calc. for $C_{28}H_{38}O_{19}$: C, 49·6; H, 5·6%).

αβ-Trehalose.—Method (*A*). The above disaccharide acetate (0·2 g.) in cold chloroform (2 c.c.) was mixed with cold dry methyl alcohol (2 c.c.) containing sodium (0·02 g.). After 5 minutes, water (10 ml.) was added and the solution neutralised to Congo-red with dilute acetic acid. The aqueous layer was evaporated under reduced pressure (50°), giving a sugar admixed with sodium acetate. Attempted crystallisation from water and alcohol being unsuccessful, the residue was dissolved in water (20 c.c.) and passed through a column of mixed Zeo-Karb and De-Acidite resins (40 g.) which was then washed with water (50 c.c.). The aqueous eluate was evaporated in a vacuum to a white ash-free residue of free sugar (0·1 g.). This recrystallised with difficulty from aqueous alcohol and then had m. p. 80° (decomp.), $[\alpha]_D^{20}$ +64° (*c*, 0·2 in water). The disaccharide did not reduce Fehling's solution or form a phenylosazone until after acid hydrolysis.

α-D-*Glucose* 2 : 3 : 4 : 6-*Tetra-acetate*.—Prepared by Georg's method (*Helv. Chim. Acta*, 1932, **15**, 932), from α-acetobromoglucose, using silver nitrate and water in ethereal solution, this had m. p. 99°, $[\alpha]_D^{20}$ +139° (*c*, 1·0 in chloroform), after several recrystallisations.

αβ-Trehalose Octa-acetate.—Method (*B*). Pure dry 2 : 3 : 4 : 6-tetra-acetyl-α-D-glucose (1·0 g.) was shaken with phosphoric oxide (1·0 g.) in dry chloroform (3 c.c.) for 68 hours in the dark at room temperature. The dark sticky residue was extracted with chloroform, and the solution concentrated to a brown syrup, which was dissolved in chloroform (15 c.c.) and ligroin (b. p. 40—60°; 15 c.c.), and chromatographed on a column of B.D.H. adsorption alumina (30 × 1·8 cm.). Two fractions so obtained had molecular weights (Rast camphor method) corresponding to that of an acetylated disaccharide: fraction (1) 0·27 g., *M*, 710; fraction (2) 0·20 g., *M*, 750. Fractions (1) and (2) were bulked and crystallised by being kept under water. The crystals were recrystallised from alcohol–water and then had $[\alpha]_D^{18}$ +64° (*c*, 0·5 in chloroform) and m. p. 118°, not depressed on admixture with the non-reducing disaccharide of m. p. 120° described above.

αβ-Trehalose.—Method (*B*). Deacetylation of the acetate with sodium methoxide, followed by crystallisation from aqueous alcohol, yielded the free sugar, $[\alpha]_D^{18}$ +70° (*c*, 0·04 in water), m. p. 80° (decomp.). The disaccharide did not reduce Fehling's solution until after hydrolysis by heating with dilute hydrochloric acid.

Attempted Synthesis of Maltose Octa-acetate.—β-D-Glucose 1 : 2 : 3 : 6-tetra-acetate (0·8 g.), silver carbonate (1·0 g.), iodine (0·2 g.), "Anhydrone" (2 g.), and β-acetofluoroglucose (1·0 g.) were shaken together in dry chloroform (10 c.c.) in the dark for 24 hours. The filtered solution was washed with sodium thiosulphate solution and water, dried, and concentrated under reduced pressure to a syrup (1·05 g.), which was chromatographed on silica (1·8 × 35 cm.), as previously described, yielding the following fractions: (1) 0·80 g., *M*, 460; (2) 0·09 g., *M*, 500; (3) 0·15 g., *M*, 900. After recrystallisation, fraction (3) had m. p. 118—120°, and m. p. mixed with *αβ*-trehalose octa-acetate (*A*) (m. p. 120°), 118—120°. Fraction (3) was deacetylated with sodium methoxide to a water-soluble free sugar, m. p. 80°, $[\alpha]_D^{20}$ +70° (*c*, 1·0 in water), which did not reduce Fehling's solution until after hydrolysis by hot dilute hydrochloric acid.

Fusion of α-Acetobromoglucose with Sodium.—The method used was analogous to that employed to synthesise *αβ*-galactobiose octa-acetate. Pure dry α-acetobromoglucose (3·0 g.) was fused in a boiling-tube at 90—100°, open to the air, and sodium pieces (0·18 g.) were added gradually. The mixture was heated at this temperature for 4½ hours, with gentle stirring, and there was no extensive decomposition. After reacetylation during one hour at 100° with sodium acetate and acetic anhydride, the solution was poured into water, and after storage extracted with chloroform. The extract was washed with water, dried, and concentrated under reduced pressure (50°) to a brown syrup (2·5 g.). Stirring this with ether gave crystals of β-glucose penta-acetate, m. p. 128° alone or mixed with authentic β-glucose penta-acetate (m. p. 130°). The ethereal solution was concentrated to a syrup (2·0 g.), *M*, 420 (Rast camphor method). Hence no disaccharide acetate was isolated from the products of this reaction.

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CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM, 15.

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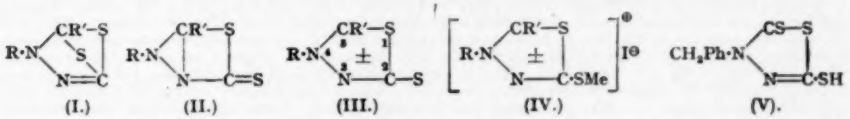
64. *Cyclic Meso-ionic Compounds. Part IV. ψ-4-Aryl-2 : 4-dihydro-2-thio-1-thia-3 : 4-diazoles* (" endo*Thiodihydrothiodiazoles* ").

By Wilson Baker, W. D. Ollis, A. Phillips, and T. Strawford.

ψ-4 : 5-Diaryl-2 : 4-dihydro-2-thio-1-thia-3 : 4-diazoles (III; R and R′ = aryl) containing chlorine have been prepared from *N*-aryl-*N*′-dithiocarboxyhydrazines, NHAr·NH·CS_2H, and aromatic acid chlorides in presence of alkali. These compounds were required for dipole moment investigation. The related 4-aryl compounds (III; R = aryl, R′ = H) were prepared in a new manner from aqueous alkaline solutions of *N*-aryl-*N*′-dithiocarboxyhydrazines and sodium dithioformate at room temperature. Benzylhydrazine and carbon disulphide gave 4-benzyl-2-mercapto-5-thio-Δ^2-1-thia-3 : 4-diazoline (V) in presence of alkali.

Compounds supposed to possess the stereochemically improbable structures (I) or (II) were first prepared by Busch and his co-workers (*Ber.*, 1895, **28**, 2635; *J. pr. Chem.*, 1899, **60**, 218, 228; 1903, **67**, 201, 216, 246, 257), who named them " *endo*thiodihydrothiodiazoles." Schönberg (*J.*, 1938, 824) preferred to represent them as monocyclic compounds containing the five-membered ring shown in (III), but possessing a hybrid structure derived from a number of dipolar forms. This view was supported by the work of Jensen and Friediger (*Kgl. Danske Videnskab. Selskab.*, 1943, **20**, 1) and of Edgerley and Sutton (forthcoming publication), who have shown that they possess high dipole moments. The nature of these and related substances which cannot be represented by simple co-valent formulæ has been discussed in earlier papers of this series (see especially Baker, Ollis, and Poole, Part I, *J.*, 1949, 311; Part III, *J.*, 1950, 1542) dealing mainly with the sydnones, and the term meso-ionic has been used there to describe such molecules. There is some difference between this method of describing the structure of these compounds and the proposals made by Schönberg; the reasons for regarding the resonance method for describing their structures as unsatisfactory were given in Part III. They are represented in, for example, the case of the " *endo*thiodihydrothiodiazoles " as shown in formula (III), and the systematic name given to the sydnones (see Part I) may be extended to these dithio-compounds which are, consequently, ψ-4-aryl-2 : 4-dihydro-2-thio-1-thia-3 : 4-diazoles.



The ψ-4-aryl-2 : 4-dihydro-2-thio-1-thia-3 : 4-diazoles (III; R = aryl, R′ = alkyl or aryl) were prepared by Busch *et al.*, by interaction of an acid chloride with the potassium salt of *N*-aryl-*N*′-dithiocarboxyhydrazine, NHAr·NH·CS_2K. We have now prepared by this method, for dipole-moment investigations, the 5-*p*-chlorophenyl-4-phenyl, 4-*p*-chlorophenyl-5-phenyl, and 4 : 5-di-*p*-chlorophenyl compounds (III). In these preparations the formation of colourless intermediates was observed which slowly passed at room temperature into the yellow ψ-thiadiazoles (III). The intermediates were not investigated, but their insolubility in water and their solubility in organic solvents show that they are not salts; they may be mixed anhydrides NHAr·NH·CS·S·CO·R′.

ψ-4-Aryl-2 : 4-dihydro-2-thio-1-thia-3 : 4-diazoles unsubstituted in position 5 (III; R = aryl, R′ = H) have previously been prepared from the potassium salts of *N*-aryl-*N*′-dithiocarboxyhydrazines by reaction with ethyl formimidate hydrochloride (Busch and Schneider, *J. pr. Chem.*, 1903, **67**, 246). It has now been found that such compounds are more readily prepared from these potassium salts by treatment with sodium dithioformate in aqueous solution at room temperature, and by this method the 4-phenyl, 4-*p*-chlorophenyl, and 4-*p*-tolyl compounds (III; R′ = H) have been prepared.

All the above ψ-thiadiazoles form methiodides which are probably best represented as containing meso-ionic cations (IV), in agreement with the views of Schönberg, and of Jensen and Friediger (*loc. cit.*).

An attempt was made to prepare ψ-4-benzyl-2 : 4-dihydro-5-methyl-2-thio-1-thia-3 : 4-diazole (III; R = CH_2Ph, R′ = Me) from benzylhydrazine by reaction with carbon disulphide

and potassium hydroxide, followed by treatment of the product with acetyl chloride. The products isolated—$C_9H_8N_2S_3$, m. p. 57°, and $C_{18}H_{14}N_4S_6$, m. p. 102°—were, however, derived only from benzylhydrazine and carbon disulphide, and were shown by direct synthesis to be 4-benzyl-2-mercapto-5-thio-Δ^2-1-thia-3 : 4-diazoline (V) and its disulphide produced by aerial oxidation. Benzylhydrazine, carbon disulphide, and alcoholic potassium hydroxide gave (V) (cf. Ziegele and Busch, *J. pr. Chem.*, 1899, **60**, 51), which when oxidised by ferric chloride gave the related disulphide previously isolated.

Experimental.

ψ-5-p-*Chlorophenyl*-2 : 4-*dihydro*-4-*phenyl*-2-*thio*-1-*thia*-3 : 4-*diazole* (III; R = Ph, R′ = *p*-C_6H_4Cl).—*p*-Chlorobenzoyl chloride (23·8 g.) was added dropwise during 2 hours to a stirred solution of the potassium salt of *N*′-dithiocarboxy-*N*-phenylhydrazine (30 g.; cf. Busch, *J. pr. Chem.*, 1899. **60**, 219) in water (200 c.c.) at room temperature. Next day the precipitate was collected and washed with hot ethanol (100 c.c.). The residue was dissolved in hot chloroform (250 c.c.), and hot ethanol (300 c.c.) added, giving *ψ*-5-p-*chlorophenyl*-2 : 4-*dihydro*-4-*phenyl*-2-*thio*-1-*thia*-3 : 4-*diazole* (12·5 g., 30%) as long, yellow, fibrous needles, m. p. 233—234° (decomp.) (Found: C, 54·8; H, 3·2; N, 9·6; S, 21·1; Cl, 11·5. $C_{14}H_9N_2S_3Cl$ requires C, 54·6; H, 3·0; N, 9·1; S, 20·8; Cl, 11·5%). The *methiodide* (cf. Busch, Kamphausen, and Schneider, *J. pr. Chem.*, 1903, **67**, 222) formed yellow plates (from ethanol–ether), m. p. 159—160° (Found: C, 40·1; H, 2·7; N, 6·3. $C_{15}H_{12}N_2S_3ClI$ requires C, 40·4; H, 2·7; N, 6·25%).

ψ-4-p-*Chlorophenyl*-2 : 4-*dihydro*-5-*phenyl*-2-*thio*-1-*thia*-3 : 4-*diazole* (III; R = *p*-C_6H_4Cl, R′ = Ph).—Reaction of benzoyl chloride (20·5 g.) with the potassium salt of *N*-*p*-chlorophenyl-*N*′-dithiocarboxyhydrazine [30 g.; see preparation of (III; R = *p*-C_6H_4Cl, R′ = H) below] in water (200 c.c.) gave a precipitate that was collected, dried, and kept in a desiccator for 5 days. Crystallisation from ethanol then gave *ψ*-4-p-*chlorophenyl*-2 : 4-*dihydro*-5-*phenyl*-2-*thio*-1-*thia*-3 : 4-*diazole* (10·5 g., 30%) as large, yellow needles, m. p. 185—187° (Found: C, 54·9; H, 3·0; N, 9·5; S, 21·2; Cl, 11·5. $C_{14}H_9N_2S_3Cl$ requires C, 54·6; H, 3·0; N, 9·1; S, 20·8; Cl, 11·5%). This compound showed a strong yellow fluorescence in ultra-violet light. The *methiodide* formed yellow plates (from chloroform–ether), m. p. 197—198° (decomp.) (Found: C, 41·0; H, 3·1; N, 5·7. $C_{15}H_{12}N_2S_3ClI$ requires C, 40·6; H, 2·7; N, 6·2%).

ψ-4 : 5-*Di*-p-*chlorophenyl*-2 : 4-*dihydro*-2-*thio*-1-*thia*-3 : 4-*diazole* (III; R = R′ = *p*-C_6H_4Cl).—In a similar manner *p*-chlorobenzoyl chloride (20·5 g.) and the potassium salt of *N*-*p*-chlorophenyl-*N*′-dithiocarboxyhydrazine (30 g.; see next paragraph) gave *ψ*-4 : 5-*di*-p-*chlorophenyl*-2 : 4-*dihydro*-2-*thio*-1-*thia*-3 : 4-*diazole* (10 g., 25%), orange plates (from *n*-butanol), m. p. 241—242° (decomp.) (Found: C, 49·9; H, 2·3; N, 8·55; S, 18·8; Cl, 20·8. $C_{14}H_8N_2S_3Cl_2$ requires C, 49·6; H, 2·4; N, 8·3; S, 18·9; Cl, 20·9%). The *methiodide* forms yellow plates (from chloroform–ether), m. p. 195—196° (decomp.) (Found: C, 37·1; H, 2·4; N, 5·5. $C_{15}H_{11}N_2S_3Cl_2I$ requires C, 37·4; H, 2·3; N, 5·8%).

ψ-4-p-*Chlorophenyl*-2 : 4-*dihydro*-2-*thio*-1-*thia*-3 : 4-*diazole* (III; R = *p*-C_6H_4Cl, R′ = H).—Carbon disulphide (9·4 c.c.) was added to a solution of *p*-chlorophenylhydrazine (20 g.) in ethanol (200 c.c.). After a few minutes, when the *p*-chlorophenylhydrazine salt of *N*-*p*-chlorophenyl-*N*′-dithiocarboxyhydrazine, $Cl{\cdot}C_6H_4{\cdot}NH{\cdot}NH{\cdot}CS_2{\cdot}NH_3{\cdot}NH{\cdot}C_6H_4Cl$, had separated, a solution of potassium hydroxide (8·6 g.) in ethanol (60 c.c.) was added. The precipitate dissolved and the crystalline potassium salt of *N*-*p*-chlorophenyl-*N*′-dithiocarboxyhydrazine separated, which was collected, washed with alcohol, then with ether, and dried. To this potassium salt in water (100 c.c.) was added sodium dithioformate (33 g.) in water (100 c.c.), and after 12 hours the crystalline precipitate (10·8 g., 31%) was collected, well washed with water, and dried. Crystallisation from ethanol (*ca.* 2 l.) gave *ψ*-4-p-*chlorophenyl*-2 : 4-*dihydro*-2-*thio*-1-*thia*-3 : 4-*diazole* as yellow platelets, m. p. 202·5° (decomp.) (Found: C, 42·4; H, 2·6; N, 12·3; Cl, 15·6; S, 28·0. $C_8H_5N_2ClS_3$ requires C, 42·0; H, 2·2; N, 12·3; Cl, 15·5; S, 28·0%).

ψ-2 : 4-*Dihydro*-4-*phenyl*-2-*thio*-1-*thia*-3 : 4-*diazole* (III; R = Ph, R′ = H).—This compound was prepared as in the previous case. To the potassium salt of *N*′-dithiocarboxy-*N*-phenylhydrazine in water (200 c.c.) was added sodium dithioformate (24 g.) in water. After 3 hours, the crystalline precipitate was collected, well washed, and crystallised from a large volume of ethanol, giving *ψ*-2 : 4-dihydro-4-phenyl-2-thio-1-thia-3 : 4-diazole (10 g., 58%) as yellow platelets, m. p. 189° [Busch, *Ber.*, 1895, **28**, 2640, gives m. p. 190° (decomp.)] (Found: C, 49·8; H, 3·1; N, 14·4. Calc. for $C_8H_6N_2S_3$: C, 49·5; H, 3·1; N, 14·4%).

ψ-2 : 4-*Dihydro*-2-*thio*-4-p-*tolyl*-1-*thia*-3 : 4-*diazole* (III; R = *p*-C_6H_4Me, R′ = H).—As in the previous cases, the potassium salt of *N*′-dithiocarboxy-*N*-*p*-tolylhydrazine (20 g.) and sodium dithioformate gave *ψ*-2 : 4-dihydro-2-thio-4-*p*-tolyl-1-thia-3 : 4-diazole. It separated from a large volume of ethanol as yellow platelets, m. p. 201° (7·7 g., 44%) (Busch, *J. pr. Chem.*, 1899, **60**, 222, gave m. p. 198°) (Found: C, 52·3; H, 3·4; N, 13·8. Calc. for $C_9H_8N_2S_3$: C, 51·9; H, 3·8; N, 13·5%).

4-*Benzyl*-2-*mercapto*-5-*thio*-Δ^2-1-*thia*-3 : 4-*diazoline* (V).—Carbon disulphide (3·8 c.c.) was added to a solution of benzylhydrazine (3 g.; Wohl and Oesterlin, *Ber.*, 1900, **33**, 2736) in ethanol (10 c.c.), and to the mixture a solution of potassium hydroxide (2·3 g.) in ethanol (10 c.c.) was added. After being heated under reflux for 8 hours, the mixture was poured into dilute hydrochloric acid and extracted with chloroform (50 c.c.), and the extract washed with water and then with 5% aqueous sodium hydrogen carbonate. Acidification of the alkaline layer and extraction with chloroform yielded a residue (4·0 g.) which solidified. Crystallisation from benzene–light petroleum (b. p. 60—80°) gave the 3 : 4-*diazoline* as thick, yellow needles, m. p. 57° (Found: C, 45·2; H, 3·3; N, 11·8; S, 39·4%; equiv., 250. $C_9H_8N_2S_3$ requires C, 45·1; H, 3·3; N, 11·7; S, 40·1%; equiv., 240).

Di-(4-benzyl-5-thio-1-thia-3 : 4-diazolin-2-yl) Disulphide.—Ferric chloride (1 g.) in water (5 c.c.) was added to the foregoing thiol (150 mg.) in ethanol (3 c.c.), and after a few minutes water was added and the product extracted into chloroform. This extract was washed with aqueous sodium hydrogen carbonate and water and then dried ($MgSO_4$), and the solvent removed, leaving a residue (135 mg., 90%) which was crystallised from chloroform (2 c.c.)–light petroleum (3 c.c.; b. p 60—80°). The *disulphide* separated as light yellow needles, m. p. 102° [Found: C, 45·5; H, 3·1; N, 11·7; S, 39·6%; *M* (Rast) 460, 490. $(C_9H_7N_2S_3)_2$ requires C, 45·2; H, 2·9; N, 11·8; S, 40·2%; *M*, 478].

THE UNIVERSITY, BRISTOL. [*Received, October 21st*, 1950.]

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65. *The Seed Fat of* Parinarium laurinum. *Part II. Component Glycerides of the Seed Fat.*

By J. P. RILEY.

The glyceride composition of the seed fat of *Parinarium laurinum* has been determined by a combination of low-temperature crystallisation and spectrophotometry. The principal glycerides are triparinarin 22%, elæostearo-diparinarin 27%, oleo-elæostearo-parinarin 16%, saturated-elæostearo-parinarin 15%, and dielæostearo-parinarin 7%. The component acids, except parinaric acid, appear to be combined in the glycerides according to the " rule of even distribution." In the case of parinaric acid, however, far more triparinarin is present than would be accounted for on either " even " or " random " distribution principles.

IN Part I of this series (*J.*, 1950, 12) the component acids of a specimen of the seed fat of *Parinarium laurinum* were shown to consist principally of parinaric (*ca.* 53%) and α-elæostearic (*ca.* 30%) acids, together with minor amounts of linoleic, oleic, and saturated and conjugated dienoic acids. In the present paper the component glycerides of the fat will be described.

The only fat containing parinaric acid whose glycerides have so far been studied is the seed fat of *Impatiens Roylei Walpers* (Kaufmann and Keller, *Ber.*, 1948, **81**, 152). These workers were able to isolate from the fat, whose mixed acids contain 42% of parinaric acid and 10% of acetic acid, a rather impure sample of acetodiparinarin. After isomerisation of the glycerides of the α-parinaric acid to the β-isomer with a trace of iodine, they were able to obtain an unstable yellow-white solid—aceto-di-β-parinarin, m. p. 66—67°—whose analysis agreed well with theory.

Oil from *P. laurinum* seeds from near Suva (Fiji) was neutralised, and the neutral oil submitted to crystallisation according to the scheme on p. 292. The seven fractions thus obtained were analysed spectrographically as described in Part I, with results which indicated that the approximate amounts of the principal component glyceride categories of the oil were (see Table II, p. 293): (*a*) no parinaro-group 6%, one 42% and two parinaro-groups 30%, triparinarin 22%; (*b*) no elæostearo-groups 26%, one 68% and two elæostearo-groups 6%; (*c*) monosaturated–diunsaturated 18%, triunsaturated 82%. Further calculation shows that the most probable principal component glycerides of the fat are: triparinarin 22%, elæostearo-diparinarin 27%, oleo-elæostearo-parinarin 16%, saturated-elæostearo-parinarin 15%, and di-elæostearo-parinarin 7%.

Continued crystallisation of the triparinarin-containing fraction (A in the scheme) yielded a glyceride fraction (J), whose mixed acids contained 95% of parinaric acid, indicating a content of at least 85% of triparinarin in the glycerides. Further attempts to purify the compound were unsuccessful owing to the extreme ease with which it polymerised.

Although the mixed acids of the fat contain only 54% of parinaric acid, there are present in the glycerides 22% of triparinarin and 6% of glycerides containing no parinaric groups. It is evident therefore that we have here an exception to the " rule of even distribution " (Hilditch, " The Chemical Constitution of Natural Fats," 2nd Edn., 1947) since the latter would predict only negligible proportions of triparinarin, and virtual absence of glycerides having no parinaric acid. The only notable exceptions to the rule so far observed among seed fats are those of *Myristica malabarica* (Collin, *J. Soc. Chem. Ind.*, 1933, **52**, 100T) which contains 16—19% of fully saturated glycerides but only 52% of saturated acids (chiefly myristic), and of *Laurus nobilis* (Collin, *Biochem. J.*, 1931, **25**, 95) in which there are 34% (wt.) of fully saturated glycerides (principally trilaurin) although its component acids contain lauric 43%, palmitic 6%, oleic 32%, and linoleic 19% (wt.). If the parinaric acid in *P. laurinum* oil were combined in

the glycerides according to a purely random distribution then there should be about 16% of triparinarin present, which is considerably less the experimentally determined amount.

On the other hand, it appears probable that the α-elæostearic and other component acids of the *Parinarium* oil are arranged in the glycerides according to the " rule of even distribution." Thus, for example, the oil contains 28% of elæostearic acid and there are present only 7% of di-elæostearo-glycerides, a figure which accords well with the graphs published by Hilditch and Seavell (*J. Oil & Colour Chemists Assoc.*, 1950, **33**, 41) relating the amounts of dilinoleo-glycerides in linolenic-rich oils to their content of linolenic acid. It is interesting that the fatty acids (other than lauric) in *Laurus nobilis* (*vide supra*) seem to be evenly distributed in the glycerides.

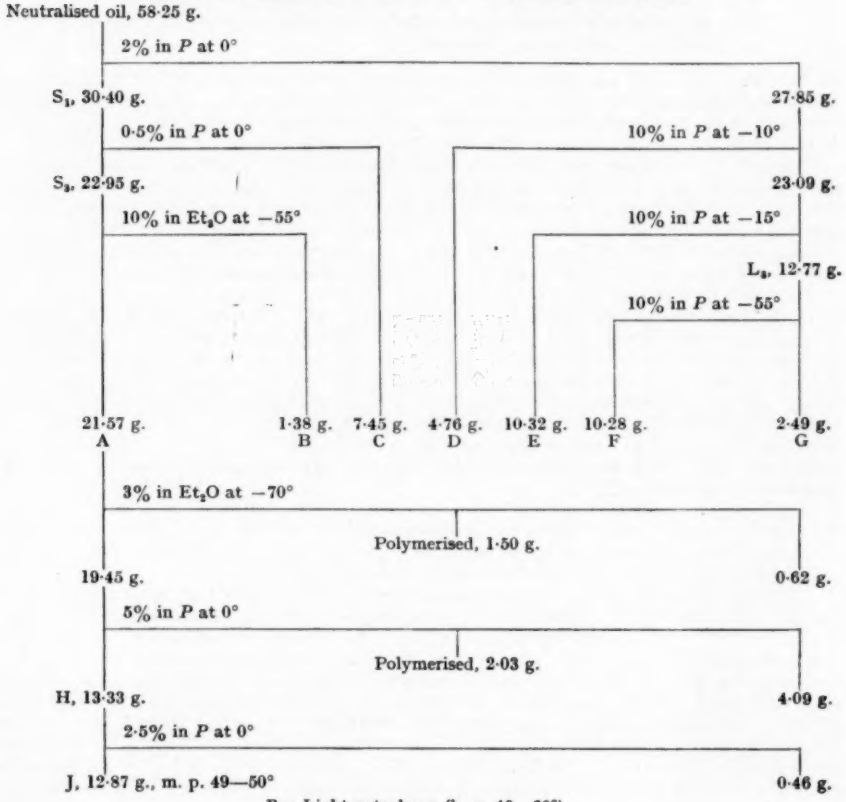
It is not yet known whether the anomalously large amount of triparinarin present in *P. laurinum* oil is due to the development of parinaric acid in a different part of the seed, or at a different time from the other acids.

Experimental.

P. laurinum seeds were extracted with light petroleum, and the resultant solid fat (yield, 12%; free acidity, 4·5%) was neutralised with alcoholic potassium hydroxide. The components of the neutralised fat were found to be parinaric 55·3%, α-elæostearic 28·3%, conjugated dienoic 1·4%, linoleic 2·0%, oleic 4·9%, saturated acids 7·2%, with unsaponifiable matter 0·9% (wt.). The neutralised fat was crystallised

Crystallisation of the mixed glycerides of P. laurinum *seed oil.*

(Soluble fractions shown on the right at each crystallisation stage.)



P = Light petroleum (b. p. 40—60°).

at low temperatures from ether and light petroleum as shown in the scheme. Samples of the fractions A—G were then analysed spectrographically for parinaric, α-elæostearic, conjugated dienoic, and linoleic acids as described in Part I (see Table I). Saturated acids and unsaponifiable matter were determined in the fractions by the Bertram (*Z. deutsch. Oel Fett Ind.*, 1925, **45**, 733) and S.P.A. (*Analyst*, 1933, **58**, 203) procedures respectively. Final calculations are in Table II.

TABLE I.

Characteristics of glyceride fractions.

Fraction.	g.	%	I.V. (Toms).	$E^{1\%}_{1cm.}$ (untreated) at * 305 mμ.	270·5 mμ.	234 mμ.	$E^{1\%}_{1cm.}$ (isomerised * at 180°/60 mins.) at 234 mμ.
A	21·57	37·0	—	2236	528	68·8	—
B	1·38	2·4	197·8	1341	659	112·0	161
C	7·45	12·7	148·4	1116	772	115·0	183
D	4·76	8·2	212·9	954	770	156·0	—
E	10·32	17·7	—	1295	777	99·9	—
F	10·28	17·7	201·4	720	894	126·0	170
G	2·49	4·3	191·4	250	675	108·6	224
Total	58·25	100·0					
H	13·33	22·9	—	2220	466	74·1	—
J	12·87	22·1	—	2491	475	62·3	—
S_1	30·40	52·2	—	1713	605	97·9	—
S_2	22·95	39·4	—	2225	557	154·0	—
L_2	12·77	21·9	212·9	642	840	110·0	176

* Expressed as acids.

TABLE II.

Component acids and glycerides of P. laurinum *fat (fractions* A—G).

	A.	B.	C.	D.	E.	F.	G.	Total.	H.	J.
Glycerides (% mol.)	37·0	2·4	12·7	8·2	17·7	17·7	4·3	100·0	—	—
Component acids of glyceride fractions (% wt.).										
Parinaric	85·2	51·1	42·5	36·4	49·4	27·4	9·5	55·3	84·6	95·0
Elæostearic	11·2	26·0	34·2	31·5	33·0	44·3	35·8	28·3	7·2	5·0
Conj. dienoic	—	2·6	1·8	5·9	0·5	1·6	2·4	1·4	1·2	—
Linoleic	—	3·8	6·3	—	—	4·4	12·9	2·0		
Oleic	0·5	7·1	6·7	23·1	10·9	6·9	31·3	4·9	7·0	—
Saturated	2·0	7·5	7·2	2·0	5·2	14·5	7·0	7·2		
Unsaponifiable	1·1	1·9	1·3	1·1	1·0	0·9	1·1	0·9		
Component acids of glyceride fractions, excluding unsaponifiable (% mol.).										
Parinaric	86·2	52·1	43·1	37·0	50·0	27·6	9·7	55·8		
Elæostearic	11·2	26·3	34·4	31·9	33·1	44·3	36·2	27·0		
Conj. dienoic	—	2·7	1·8	6·0	0·5	1·6	2·4	1·3		
Linoleic	—	3·9	6·3	—	—	4·3	12·9	2·2		
Oleic	0·5	7·1	6·8	23·0	10·9	6·9	31·4	7·6		
Saturated	2·1	7·9	7·6	2·1	5·5	15·3	7·4	6·1		
Component glyceride categories of fractions (increments % mol.).										
(*a*) No parinaro-	—	—	—	—	—	3·0	3·0	6·0		
Monoparinaro-	—	1·0	9·0	7·3	8·8	14·7	1·3	42·1		
Diparinaro-	15·3	1·4	3·7	0·9	8·9	—	—	30·2		
Triparinarin	21·7	—	—	—	—	—	—	21·7		
(*b*) No Elæostearo-	24·6	0·5	—	0·3	0·1	—	—	25·5		
Monoelæostearo-	12·4	1·9	12·3	7·9	17·6	11·9	3·9	67·9		
Dielæostearo-	—	—	0·4	—	—	5·8	0·4	6·6		
(*c*) Monosatd.-diunsatd.	2·3	0·6	2·9	0·5	2·9	8·1	1·0	18·3		
Triunsaturated	34·7	1·8	9·8	7·7	14·8	9·6	3·3	81·7		

The author thanks Professor T. P. Hilditch, F.R.S., and Dr. M. L. Meara for their advice and valuable criticism, and Mr. G. Winter of the Defence Research Laboratory, Victoria, Australia, for a gift of seeds.

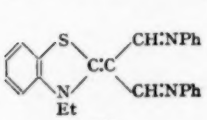
THE UNIVERSITY, LIVERPOOL. [*Received, October 23rd*, 1950.]

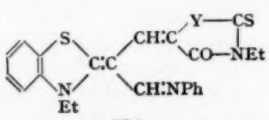
66. *Some Trinuclear Cyanine Dyes. Part IV. The Action of Acid on Dinuclear Intermediate Dyes.*

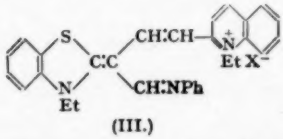
By Frances M. Hamer.

Of seven dinuclear intermediate dyes having the group :C(CH:)(CH:NPh) four gave hydrochlorides * having the group ·C(CH:)=CH·NHPh ; on more drastic treatment with acid, three gave the corresponding dimethin*mero*cyanine having the chain :CH·CH:. Five dinuclear intermediate dyes having the group :C(CH:CH·)(CH:NPh) gave perchlorate hydroperchlorates having the group ·C(CH:CH·)=CH·NHPh ; on more drastic treatment with acid, four gave the corresponding trimethincyanines having the chain :CH·CH:CH.

Dinuclear intermediate dyes were obtained by condensing one mol. of a heterocyclic dianil, such as (I), with one mol. of a compound having a reactive methylene group, whereas condensation with two mols. gave the trinuclear dyes themselves (Hamer, Rathbone, and Winton, *J.*, 1947, 1434; 1948, 1872; 1949, 1113). According as the reactive methylene groups were

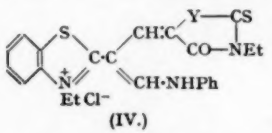

(I.)

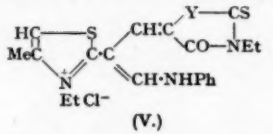

(II.)

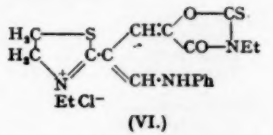

(III.)

cyclic or in the form of external methyl groups, these intermediate compounds, *e.g.*, (II) and (III), fell into two classes, which are characterised, in one of the resonating structures, by the chains :C(CH:)(CH:NPh) and :C(CH:CH·)(CH:NPh), respectively. In recording the absorption maxima of acid and of alkaline solutions of all the intermediate dyes and in determining the pH range of the colour change in nine instances, it was noted that more drastic treatment with acid produced an irreversible colour change (*idem*, *J.*, 1948, 1872; 1949, 1113), which was not further investigated at that time.

The intermediate compound (II; Y = S), and three others, all having the chain :C(CH:)(CH:NPh) (*idem*, *J.*, 1949, 1113), have now been converted into well crystallising hydrochlorides * (IV;


(IV.)


(V.)

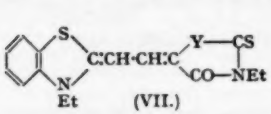

(VI.)

Y = S), (V; Y = NPh or S), and (VI), possessing, in one of the resonating structures, the chain ·C(CH:)=CH·NHPh. The absorption maxima of methyl-alcoholic solutions of these hydrochlorides are the same as those already recorded for acidified solutions of the bases (*loc. cit.*, 1949). Nor is there anything fresh to record regarding sensitising action, since it is known that dye

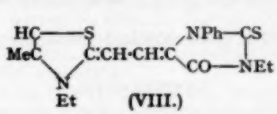
* The compounds are termed hydrochlorides because they are formed by addition of hydrochloric acid, although in the particular resonating structure formulated both nitrogen atoms are in fact quaternary. The same applies to the hydroperchlorates.

bases and their hydrochlorides appear to reach an equilibrium depending on the pH of the photographic emulsion. Attempts to acetylate two of the hydrochlorides were unsuccessful.

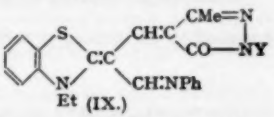
A dye now obtained from the first intermediate compound (II; Y = S), by more drastic treatment with hydrochloric acid, has been identified as the known dimethin*mero*cyanine (VII; Y = S) (Hamer and Winton, *J.*, 1949, 1126). Similarly, such more drastic treatment of the second intermediate compound yielded the dimethin*mero*cyanine (VIII), which is here described. In the third instance, more drastic treatment with acid still gave the hydrochloride (V; Y = S), and not the corresponding dimethin*mero*cyanine; in the fourth, the hydrochloride (VI) was destroyed but the related dimethin*mero*cyanine was not obtained. On the other hand the 5-chloro-derivative of the intermediate compound (II; Y = NPh) did not give the 5-chloro-derivative of the hydrochloride (IV; Y = NPh) but readily yielded the 5-chloro-derivative of the dimethin*mero*cyanine (VII; Y = NPh). The observed lower melting point and mixed melting point of a specimen now prepared by the synthetic method, as compared with that prepared from the anilomethyl compound, has been confirmed but is not explained.



(VII.)



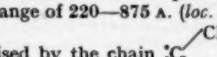
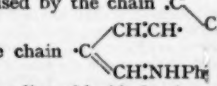
(VIII.)

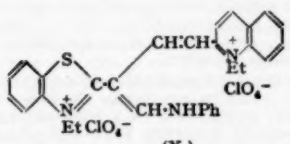


(IX.)

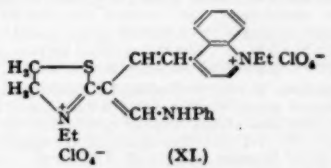
The hydrolysis which occurs with three of five of the above dinuclear intermediate dyes is of an unusual type, consisting in replacement by a hydrogen atom of the group ·CH:NPh, which is attached to the dimethin chain of the parent substances.

Two new anilomethyl compounds were made, namely (IX; Y = Ph) and its *p*-sulpho-derivative (IX; Y = *p*-C_6H_4·SO_3H), but neither gave a hydrochloride, presumably, like the 5-chloro-derivative of (II; Y = NPh) which also failed to give one, because of their electro-negative character. The first of the new anilomethyl compounds was so unstable to acid that the absorption maximum of its acidified methyl-alcoholic solution could not be determined, but neither it nor its *p*-sulpho-derivative underwent a smooth conversion into the corresponding dimethin*mero*cyanine. The bathochromic shift, 940 A., on passing from (IX; Y = Ph) to the parent dimethin*mero*cyanine lies outside the range, −30 to 705 A., previously recorded for 14 such compounds (Hamer, Rathbone, and Winton, *J.*, 1949, 1113), as does that of (IX; Y = *p*-C_6H_4·SO_3H), where it is 1015 A. for alkaline and 1795 A. for acid methyl-alcoholic solutions. With (IX; Y = *p*-C_6H_4·SO_3H) itself, the hypsochromic shift on passing from base to acid salt is 120 A., which again lies outside the earlier range of 220—875 A. (*loc. cit.*).

Of dinuclear intermediate dyes characterised by the chain  , it was hoped to prepare hydrochlorides, characterised by the chain  in one resonating form. Therefore (III; X = Cl), as also the corresponding chloride having a benzthiazolium in place of a 2-quinolinium nucleus, were prepared, earlier compounds of this type having been confined to iodides and perchlorates (*idem*, *J.*, 1948, 1872). Hydrochlorides did not separate but the



(X.)



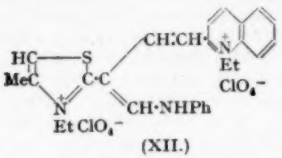
(XI.)

perchlorate hydroperchlorate * (X) could be precipitated and, similarly, its analogue having a benzthiazolium in place of a 2-quinolinium nucleus. From dinuclear intermediate dye iodides, which have already been described (*loc. cit.*), three other such hydroperchlorates were prepared, namely (XI), its analogue having a benzthiazolium in place of a 4-quinolinium nucleus, and (XII).

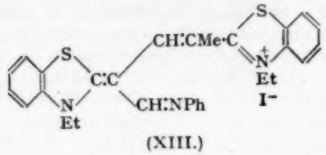
From the chloride (III; X = Cl), more drastic treatment with hydrochloric acid, followed

* See footnote, p. 294.

by potassium perchlorate, yielded a dye perchlorate, which was identified as the unsubstituted parent trimethincyanine. Three dinuclear intermediate dye iodides similarly underwent conversion into the corresponding unsubstituted trimethincyanine perchlorates. Thus in this

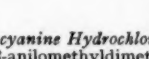


(XII.)



(XIII.)

series also, acid under the more drastic conditions replaces by a hydrogen atom the group ·CH:NPh, which here is attached to the trimethin chain.

A dinuclear intermediate compound (XIII), characterised by the group  , was prepared by condensing (I) with 2-ethylbenzthiazole ethiodide; it was unstable to light.

Experimental.

[5-(3-*Ethylrhodanine*)][2-(3-*ethylbenzthiazoline*)]-β-*anilomethyldimethin*mero*cyanine Hydrochloride* (IV; Y = S).—On treating [5-(3-ethylrhodanine)][2-(3-ethylbenzthiazoline)]-β-anilomethyldimethin*mero*cyanine (II; Y = S) (1·46 g.) with concentrated hydrochloric acid (2 c.c.), the red solid became orange. Alcohol (10 c.c.) was added and the mixture heated and then cooled. The washed crystals (1·54 g.) were recrystallised from a mixture of water (35 c.c.), alcohol (35 c.c.), and hydrochloric acid (3·5 c.c.), and the yield was 81%. After a second recrystallisation from a mixture of water (55 c.c. per g.), methyl alcohol (55 c.c. per g.), and hydrochloric acid (5 c.c. per g.), the yield was 66% (Found, on a sample dried in a vacuum at 60—80°: Cl, 7·25. $C_{23}H_{22}ON_2ClS_2$ requires Cl, 7·25%). The orange crystals darkened from 180° and had m. p. 189° (decomp.). An attempt to acetylate this dye by boiling acetic anhydride was unsuccessful.

[5-(3-*Ethylrhodanine*)][2-(3-*ethylbenzthiazoline*)]*dimethin*mero*cyanine* (VII; Y = S).—A mixture of [5-(3-ethylrhodanine)][2-(3-ethylbenzthiazoline)]-β-anilomethyldimethin*mero*cyanine (II; Y = S) (1 g.) with alcohol (16 c.c.) and concentrated hydrochloric acid (4 c.c.) was boiled for 2 hours. The resultant washed dye (82%), after recrystallisation from benzene (430 c.c. per g.), gave a 54% yield, and after a second recrystallisation from pyridine (40 c.c. per g.), a 42% yield [Found, in a sample dried in a vacuum at 80—100° (which method of drying was used also in other analyses unless otherwise stated): S, 27·3. Calc. for $C_{16}H_{16}ON_2S_2$: S, 27·6%]. Samples of this substance, of a synthetic specimen (Hamer and Winton, *J.*, 1949, 1126), and of their mixture melted simultaneously at 265° (decomp.), with previous darkening.

[5-(3-*Ethyl*-1-*phenyl*-2-*thiohydantoin*)][2-(3-*ethyl*-4-*methyl*-Δ⁴-*thiazoline*)]-β-*anilomethyldimethin*mero*cyanine Hydrochloride* (V; Y = NPh).—A suspension of [5-(3-ethyl-1-phenyl-2-thiohydantoin)][2-(3-ethyl-4-methyl-Δ⁴-thiazoline)]-β-anilomethyldimethin*mero*cyanine (1 g.) in alcohol (4 c.c.) was treated with concentrated hydrochloric acid (2 c.c.), and the mixture cooled. Dissolution, followed by crystallisation, occurred. The washed crystals (1·09 g.) were twice recrystallised from methyl alcohol (10 c.c. per g.), with hydrochloric acid (5 drops per g.) and water (5 c.c. per g.), after which the yield was 61% (Found: Cl, 7·0. $C_{28}H_{27}ON_4ClS_3$ requires Cl, 6·95%). The yellow crystals had m. p. 165° (decomp.), with darkening from 135°.

[5-(3-*Ethyl*-1-*phenyl*-2-*thiohydantoin*)][2-(3-*ethyl*-4-*methyl*-Δ⁴-*thiazoline*)]*dimethin*mero*cyanine* (VIII).—After the original filtrate from the preceding preparation had been heated for 15 minutes, precipitation with aqueous ammonia gave a 4% yield of this dimethin*mero*cyanine (1% after recrystallisation). In another experiment, the reaction mixture was boiled for 10 minutes and the resultant dye (1·35 g., 86%) recrystallised from methyl alcohol (500 c.c.), giving a 59% yield (Found: S, 17·45. $C_{18}H_{21}ON_3S_3$ requires S, 17·3%). The red crystals had m. p. 240° (decomp.), with previous shrinking and darkening. A specimen synthesised as follows melted simultaneously, as did their mixture.

A mixture of 3-ethyl-1-phenyl-2-thiohydantoin (1·10 g., 1 mol.), 2-β-acetanilidovinyl-4-methylthiazole ethiodide (1 mol.), triethylamine (2 mols.), and absolute alcohol (20 c.c.) was boiled for 15 minutes. After recrystallisation of the washed product (1·63 g.) from methyl alcohol (600 c.c.), the yield was 69% (Found: S, 17·4%). The absorption maximum previously quoted (*J.*, 1949, 1113) was provided by Dr. L. G. S. Brooker and Mr. F. L. White.

[2-(3-*Ethyl*-4-*methyl*-Δ⁴-*thiazoline*)][5-(3-*ethylrhodanine*)]-α-*anilomethyldimethin*mero*cyanine Hydrochloride* (V; Y = S).—A suspension of [2-(3-ethyl-4-methyl-Δ⁴-thiazoline)][5-(3-ethylrhodanine)]-α-anilomethyldimethin*mero*cyanine (0·83 g., 1 mol.) in cold alcohol (20 c.c.) was treated with concentrated hydrochloric acid (2 c.c., 10 mols.). From the resultant orange solution dye began to crystallise. Water (20 c.c.) was added and the washed *hydrochloride* (0·82 g.) was recrystallised from methyl alcohol (40 c.c.) and obtained in 72% yield (Found, on a sample dried in a vacuum at 60—80°: Cl, 7·85. $C_{20}H_{22}ON_2ClS_2$ requires Cl, 7·85%). The orange crystals had m p. 268° (decomp.). Attempted acetylation with acetic anhydride was unsuccessful.

For the above preparation I thank Dr. R. J. Rathbone.

When the original reaction mixture was boiled for 30 minutes, the *hydrochloride* was obtained as before, in undiminished yield.

[5-(3-*Ethyl*-4-*keto*-2-*thio*-*oxazolidine*)][2-(3-*ethylthiazolidine*)]-β-*anilomethyldimethin*mero*cyanine Hydrochloride* (VI).—A suspension of [5-(3-ethyl-4-keto-2-thio-oxazolidine)][2-(3-ethylthiazolidine)]-β-anilomethyldimethin*mero*cyanine (1 g.) in hot alcohol (10 c.c.), on treatment with hot concentrated hydrochloric acid solution (2 c.c.), gave a solution which deposited a 91% yield of *hydrochloride*. After recrystallisation from methyl alcohol (10 c.c.), containing concentrated hydrochloric acid (4 drops), the yield was 63% (Found : Cl, 8·3. $C_{19}H_{22}O_2N_3ClS_3$ requires Cl, 8·35%). The deep yellow crystals melted at 192—202° (decomp.), the exact point depending on the rate of heating.

The effect of boiling the original solution was to destroy the hydrochloride but the dimethin*mero*cyanine (Hamer and Winton, *J.*, 1949, 1126) was not isolated.

[5-(3-*Ethyl*-1-*phenyl*-2-*thiohydantoin*)][2-(5-*chloro*-3-*ethylbenzthiazoline*)]*dimethin*mero*cyanine*.—In an attempt to prepare its hydrochloride, [5-(3-ethyl-1-phenyl-2-thiohydantoin)][2-(5-chloro-3-ethylbenzthiazoline)]-β-anilomethyldimethin*mero*cyanine (1 g.) was suspended in alcohol (4 c.c.), and concentrated hydrochloric acid was stirred in, with ice-cooling, but the resultant deep-red solution deposited tar.

In an experiment where the reaction mixture was boiled for 20 minutes, an 81% yield of the *dimethin*mero*cyanine* crystallised; after recrystallisation from pyridine (8 c.c. per g.), the yield was 60% (Found : Cl, 8·0; S, 14·55. $C_{32}H_{26}ON_5ClS_3$ requires Cl, 8·05; S, 14·5%). The vermilion crystals had m. p. at about 230° (decomp.), with previous darkening and shrinking. A sample synthesised as below had an identical absorption curve and photographic sensitising properties but melted at about 220° (decomp.), whilst the mixture melted at about 208° (decomp.).

A mixture of 3-ethyl-1-phenyl-2-thiohydantoin (2·20 g., 1 mol.), 2-β-acetanilidovinyl-5-chlorobenzthiazole ethiodide (1 mol.), triethylamine (2 mols.), and absolute alcohol (50 c.c.) was boiled and stirred for 5 minutes. The washed product (3·53 g.), after recrystallisation from benzene (50 c.c.), resulted in 65% yield and, after a second recrystallisation from benzene and light petroleum (b. p. 60—80°; 80 c.c. of each), in 55% yield (Found : Cl, 8·1; S, 14·4%). The absorption maximum previously quoted (*J.*, 1949, 1113) was provided by Dr. L. G. S. Brooker and Mr. F. L. White.

[4-(3-*Methyl*-1-*phenyl*-5-*pyrazolone*)][2-(3-*ethylbenzthiazoline*)]-β-*anilomethyldimethin*mero*cyanine* (IX; Y = Ph).—3-Ethyl-2-dianilo*iso*propylidenebenzthiazoline (1·92 g., 1 mol.) and 3-methyl-1-phenyl-5-pyrazolone (1 mol.) in pyridine (20 c.c.) were heated together at 50—60° for 10 minutes. The substance precipitated in 78% yield by absolute ether (100 c.c.) was recrystallised from pyridine (5 c.c. per g.) and obtained in 53% yield (Found : S, 7·0. $C_{31}H_{34}ON_4S$ requires S, 6·9%). The reddish-orange dye had m. p. 205° (decomp.). The absorption maximum of its methyl-alcoholic solution containing ammonia was at 3930 A. One containing sulphuric acid (1 g. in 100 c.c.) was orange but faded to yellow before the absorption measurements could be made. The substance was photographically inert.

[4-(3-*Methyl*-1-*phenyl*-5-*pyrazolone*)][2-(3-*ethylbenzthiazoline*)]*dimethin*mero*cyanine*.—3-Methyl-1-phenyl-5-pyrazolone (0·87 g., 1 mol.), 2-β-acetanilidovinylbenzthiazole ethiodide (1 mol.), triethylamine (1·1 mols.), and absolute alcohol (15 c.c.) were boiled and stirred together for 5 minutes. The washed product (96% yield) was recrystallised from benzene and light petroleum (b. p. 60—80°; 100 c.c. of each per g.), leaving a very little thiacarbocyanine undissolved, and giving an 89% yield. After a second such recrystallisation, the yield was 81% (Found : S, 9·2. $C_{31}H_{28}ON_4S$ requires S, 8·85%). The red crystals had m. p. about 204° (decomp.), with previous darkening and softening. The absorption maximum of a methyl-alcoholic solution was at 4870 A. The sensitising maximum lay at 5200 A.

[4-(3-*Methyl*-1-p-*sulphophenyl*-5-*pyrazolone*)][2-(3-*ethylbenzthiazoline*)]-β-*anilomethyldimethin*mero*cyanine* (IX; Y = *p*-$C_6H_4{\cdot}SO_3H$).—3-Methyl-1-*p*-sulphophenyl-5-pyrazolone (1·27 g., 1 mol.), which had been rendered anhydrous in a vacuum at 100° (cf. Möllenhof, *Ber.*, 1892, **25**, 1941) was heated at 50—60° for 10 minutes with 2-dianilo*iso*propylidene-3-ethylbenzthiazoline (1 mol.) and pyridine (10 c.c.). The product precipitated by absolute ether (100 c.c.) was washed with ether, ground with water (15 c.c.), and further thoroughly washed with water (Found : S, 11·55. $C_{31}H_{34}O_4N_4S_3$ requires S, 11·8%). The vermilion crystals had m. p. at about 240° (decomp.) with darkening from about 180°. Their methyl-alcoholic solution containing ammonia had its absorption maximum at 3875 A. and one containing sulphuric acid had the maximum at 3755 A. Towards a gelatino bromide photographic plate the dye was inert but it sensitised a gelatino chloride plate weakly to 5300 A.

[4-(3-*Methyl*-1-p-*sulphophenyl*-5-*pyrazolone*)][2-(3-*ethylbenzthiazoline*)]*dimethin*mero*cyanine*.—To a mixture of anhydrous 3-methyl-1-*p*-sulphophenyl-5-pyrazolone (1·27 g., 1 mol.) and 2-β-acetanilidovinylbenzthiazole ethiodide (1 mol.) in absolute alcohol (25 c.c.) was added triethylamine (2·2 mols.), and the whole was boiled and stirred for 5 minutes. The solvent was removed under a vacuum and the residual red tar dissolved in hot water (15 c.c.) and treated with acetic acid. To remove a trace of thiacarbocyanine from the washed dye (77% yield), it was ground with 8½% ammonia solution (10 c.c.); the filtered solution was evaporated to remove excess of ammonia, diluted with water, and acidified with acetic acid. After cooling, filtering off, and washing, the yield was 64% (Found : S, 14·85. $C_{31}H_{34}O_4N_4S_3$ requires S, 14·55%). The purplish solid remained unmelted at 290°. The absorption maximum of a methyl-alcoholic solution containing ammonia was at 4890 A. and that of one containing sulphuric acid was at 5550 A., with a secondary maximum at 4350 A. The sensitising maximum was at 5900 A.

[2-(1-*Ethylquinoline*)][2-(3-*ethylbenzthiazole*)]-γ-*anilomethyltrimethincyanine Chloride* (III; X = Cl).—A mixture of 2-dianilo*iso*propylidene-3-ethylbenzthiazoline (3·83 g., 1 mol.), quinaldine ethochloride (1 mol.), and pyridine (20 c.c.) was heated at 60—70° for 20 minutes. Recrystallisation of the washed dye (3·27 g.) from ethyl alcohol (30 c.c.) gave a 50% yield and, after a second recrystallisation, 36% (Found : Cl, 7·1. $C_{36}H_{34}N_3ClS$ requires Cl, 7·1%). The dark purplish crystals had m. p. at about 175° (decomp.).

[2-(1-*Ethylquinoline*)][2-(3-*ethylbenzthiazole*)]-γ-*anilomethyltrimethincyanine Perchlorate Hydroperchlorate* (X).—On treatment of the deep-purple suspension of the preceding chloride (0·20 g.) in absolute alcohol (1 c.c.) with concentrated hydrochloric acid (0·2 c.c.), an orange solution resulted. Addition of a solution of sodium perchlorate (0·20 g.) in water (2 c.c.) precipitated the *hydroperchlorate* in 86% yield. It was recrystallised by dissolving it in boiling methyl alcohol and adding 60% perchloric acid (1 drop per c.c. of methyl alcohol), giving a 49% yield. After a second such recrystallisation the yield was 38%. This and subsequent compounds were dried for microanalysis at 56°/0·4 mm. unless otherwise stated (Found: N, 6·4. $C_{30}H_{33}O_8N_3Cl_2S$ requires N, 6·35%). The orange crystals had m. p. 264° (decomp.), with previous darkening and shrinking.

[2-(1-*Ethylquinoline*)][2-(3-*ethylbenzthiazole*)]*trimethincyanine Perchlorate.*—The dye chloride (0·50 g.) was boiled for 30 minutes with hydrochloric acid (2 N.; 5 c.c.), and the hot solution treated with one of sodium perchlorate (1 g.) in water (5 c.c.), and then with aqueous ammonia. After two digestions with water to remove neocyanine, the residue amounted to a 49% yield. On recrystallisation from methyl alcohol (250 c.c. per g.), the yield dropped to 23%, and on a second recrystallisation to 8% (Found: Cl, 7·65. $C_{23}H_{23}O_4N_2ClS$ requires Cl, 7·75%). The dark blue crystals had m. p. 272° (decomp.). Their alcoholic solution was identical in colour with one of the corresponding dye iodide (Beilenson, Fisher, and Hamer, *Proc. Roy. Soc.*, 1937, *A*, **163**, 138).

[*Bis*-2-(3-*ethylbenzthiazole*)]-α-*anilomethyltrimethincyanine Chloride.*—A mixture of 2-dianiloisopropylidene-3-ethylbenzthiazoline (3·83 g., 1 mol.), 2-methylbenzthiazole ethochloride (1 mol.), and pyridine (20 c.c.) was heated at 60—70° for 5 minutes. The tar obtained by precipitation with absolute ether (160 c.c.) was washed with ether and treated with hot water (36% yield). It was dissolved in hot absolute alcohol (6 c.c.) and treated with ethyl acetate (15 c.c.), giving a 24% yield. After a second such recrystallisation, the yield was 18% (Found: Cl, 7·0. $C_{28}H_{26}N_2ClS_2$ requires Cl, 7·05%). The dark bronze substance had m. p. at about 174° (decomp.), with previous darkening.

[*Bis*-2-(3-*ethylbenzthiazole*)]-α-*anilomethyltrimethincyanine Perchlorate Hydroperchlorate.*—On treatment of a suspension of the preceding chloride (0·20 g.) in ethyl alcohol (1 c.c.) with concentrated hydrochloric acid (0·2 c.c.), dissolution occurred. A solution of sodium perchlorate (0·20 g.) in water (2 c.c.) precipitated the *hydroperchlorate* in 94% yield. Dissolution in hot methyl alcohol (30 c.c.) with subsequent addition of 60% perchloric acid (1 drop per c.c.) gave a 64% yield (Found: N, 6·4. $C_{28}H_{27}O_8N_2Cl_3S_2$ requires N, 6·3%). The maroon crystals had m. p. 254° (decomp.), with previous darkening.

[4-(1-*Ethylquinoline*)][2-(3-*ethyl*-Δ^2-*thiazoline*)]-γ-*anilomethyltrimethincyanine Perchlorate Hydroperchlorate* (XI).—When the bluish-purple suspension of [4-(1-ethylquinoline)][2-(3-ethyl-Δ^2-thiazoline)]-γ-anilomethyltrimethincyanine iodide (0·2 g.) in alcohol (1 c.c.) was treated with concentrated hydrochloric acid (0·2 c.c.), the colour reddened. The solution obtained on heating was treated with one of sodium perchlorate (0·2 g.) in hot water (2 c.c.). The washed *hydroperchlorate* (79% yield) was recrystallised by dissolving it in hot methyl alcohol (60 c.c.) and adding 60% perchloric acid (1 drop per c.c.), giving a 53% yield (Found: N, 6·65. $C_{36}H_{39}O_8N_3Cl_4S$ requires N, 6·85%). The crimson crystals had m. p. 228° (decomp.).

[4-(1-*Ethylquinoline*)][2-(3-*ethyl*-Δ^2-*thiazoline*)]*trimethincyanine Perchlorate.*—The clear red solution obtained by heating [4-(1-ethylquinoline)][2-(3-ethyl-Δ^2-thiazoline)]-γ-anilomethyltrimethincyanine iodide (1·00 g.) with dilute hydrochloric acid (20 c.c.; 2N.) became very pale when boiled for 1 minute. The solution was treated hot with one of sodium perchlorate (2 g.) in water (5 c.c.). Addition of aqueous ammonia precipitated a tar, which stiffened on cooling; after decantation of the liquid, it was washed with cold water. Whilst still wet, it was boiled with methyl alcohol (4 c.c.), and hot filtration left a crystalline residue (0·25 g., 33%). Recrystallisation from methyl alcohol (120 c.c. per g.) gave a 12% yield and, a second recrystallisation, 4% (Found: N, 6·6. $C_{19}H_{23}O_4N_2ClS$ requires N, 6·8%). The dark violet crystals had no definite m. p.; shrinking began at about 212° and progressive decomposition became violent at about 245—253°. The colours of alcoholic solutions of this *perchlorate* and the corresponding iodide (Hamer, Rathbone, and Winton, *J.*, 1948, 1872) were identical.

[2-(3-*Ethyl*-Δ^2-*thiazoline*)][2-(3-*ethylbenzthiazole*)]-α-*anilomethyltrimethincyanine Perchlorate Hydroperchlorate.*—[2-(3-Ethyl-Δ^2-thiazoline)][2-(3-ethylbenzthiazole)]-α-anilomethyltrimethincyanine iodide was suspended in alcohol, heated with concentrated hydrochloric acid, and then treated with aqueous sodium perchlorate solution. The washed *hydroperchlorate* (0·12 g., 44%) was recrystallised by means of methyl alcohol (37 c.c.), with later addition of 60% perchloric acid (37 drops), giving a 33% yield (Found: N, 6·65. $C_{34}H_{37}O_8N_3Cl_2S_2$ requires N, 6·75%). The bright reddish-orange crystals had m. p. 253° (decomp.), with previous darkening and shrinking.

When the original dye iodide (0·2 g.) was boiled with dilute hydrochloric acid (5 c.c.; 2N.) for 5 minutes, decomposition occurred; lessening the time of heating did not yield a clean product.

[2-(1-*Ethylquinoline*)][2-(3-*ethyl*-4-*methylthiazole*)]-γ-*anilomethyltrimethincyanine Perchlorate Hydroperchlorate* (XII).—From [2-(1-ethylquinoline)][2-(3-ethyl-4-methylthiazole)]-γ-anilomethyltrimethincyanine iodide in alcohol with hydrochloric acid, followed by sodium perchlorate, a 69% yield (0·21 g.) of washed *hydroperchlorate* was obtained. Recrystallisation by use of methyl alcohol (35 c.c.), followed by 60% perchloric acid (35 drops), gave a 46% yield (Found: N, 6·95. $C_{37}H_{39}O_8N_3Cl_2S$ requires N, 6·7%). The purple crystals had m. p. 264° (decomp.).

[2-(1-*Ethylquinoline*)][2-(3-*ethyl*-4-*methylthiazole*)]*trimethincyanine Perchlorate.*—Dilute hydrochloric acid (12 c.c.; 2N.) was added to [2-(1-ethylquinoline)][2-(3-ethyl-4-methylthiazole)]-γ-anilomethyltrimethincyanine iodide (0·5 g.). The resultant red solid dissolved when the mixture was heated; the solution was boiled for 5 minutes and then treated with a hot solution of sodium perchlorate (1 g.) in water (5 c.c.). Addition of aqueous ammonia precipitated the *dye*, which was filtered off when cold and well

washed with water (84% yield). After recrystallisation from methyl alcohol (250 c.c. per g.), the yield was 39% (Found: C, 56·7; H, 5·5; Cl, 8·5. $C_{29}H_{32}O_4N_4ClS$ requires C, 56·8; H, 5·5; Cl, 8·4%). The dark green crystals had m. p. 263° (decomp.). Their alcoholic solution was identical in colour with that of the corresponding dye iodide (Hamer, Rathbone, and Winton, *J.*, 1948, 1872).

[4-(1-*Ethylquinoline*)][2-(3-*ethyl*-4-*methylthiazole*)]*trimethincyanine Perchlorate*.—By boiling [4-(1-ethylquinoline)][2-(3-ethyl-4-methylthiazole)]-γ-anilomethyltrimethincyanine iodide with dilute hydrochloric acid and treating the solution with sodium perchlorate and ammonia, a 95% yield of dye *perchlorate* resulted. Recrystallisation from methyl alcohol (120 c.c. per g.) gave a 56% yield, which dropped to 35% after a further recrystallisation (Found: C., 8·15. $C_{30}H_{33}O_4N_4ClS$ requires Cl, 8·4%). The dark blue crystals had m. p. 233° (decomp.). Their alcoholic solution was identical in colour with one of the corresponding dye iodide (*loc. cit.*).

[*Bis*-2-(3-*ethylbenzthiazole*)]-α-*anilomethyl*-γ-*methyltrimethincyanine Iodide* (XIII).—A mixture of 2-dianil*oiso*propylidene-3-ethylbenzthiazoline (1·9 g., 1 mol.), 2-ethylbenzthiazole ethiodide (1 mol.), and pyridine (10 c.c.) was heated at 60—65° for 5 minutes. A tar precipitated by absolute ether (70 c.c.) was, after being washed with ether, converted into a solid by treatment with water (80 c.c.). After dissolution of the product (2·60 g.) in 50% aqueous methyl alcohol (30 c.c.) and treatment with water (50 c.c.), the yield was 58% and, after a second such purification, 43% (Found, on a sample dried in a vacuum at 80—100°: I, 20·65. $C_{29}H_{33}N_3IS_2$ requires I, 20·85%). The maroon substance underwent violent decomposition at 194—196°, with darkening from 130°. Absorption curves were difficult to obtain. A freshly prepared methyl-alcoholic solution containing pyridine had the maximum at 5420 A., but one containing sulphuric acid faded too quickly for the maximum in the visible region to be recorded.

This preparation was carried out by Mrs. S. Palling, to whom I am indebted.

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IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
SOUTH KENSINGTON, LONDON, S.W.7. [*Received, September 28th*, 1950.]

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67. *Organic Compounds of Platinum. Part I. The Preparation and Constitution of Trimethylplatinum Compounds.*

By M. E. Foss and (the late) C. S. GIBSON.

A convenient method of obtaining trimethylplatinum compounds is described which starts from the readily accessible and non-hygroscopic *cis*-dipyridinotetrachloroplatinum. This compound with methylmagnesium iodide gives a 70% yield of the dimer $[Me_3Pt\,pyI]_2$, a halogen-bridged compound converted by more pyridine into the known $Me_3Pt\,py_2I$. One molecule of pyridine is removed from the latter dipyridine complex by dilute acid, to regenerate the monopyridine complex, the second molecule is more firmly bound, but is displaced when the dimer reacts in chloroform with excess of ethylenediamine, the compound $2Me_3PtI,3en$ crystallising. The last reacts with hydriodic acid to give trimethylplatinum iodide.

In tetrameric $[Me_3PtCl]_4$ each platinum atom has an octahedral configuration and the three methyl groups linked to it are *cis* to one another. It is suggested that the same arrangement persists in the above co-ordination compounds, which are formulated accordingly. The inability to prepare trimethylplatinum compounds from *trans*-dipyridinotetrachloroplatinum lends support to this view.

THE first organic compound of platinum, trimethylplatinum iodide, was prepared in 1909 by treatment of anhydrous platinum tetrachloride with methylmagnesium iodide (Pope and Peachey, *J.*, **95**, 571). Trimethylplatinum compounds have since been investigated by Menzies *et al.* (*J.*, 1928, 565; 1933, 21; 1933, 1250; 1949, 1168), Gilman and Lichtenwalter (*J. Amer. Chem. Soc.*, 1939, **61**, 957), Lichtenwalter (*Iowa State Coll. J. Sci.*, 1939, **14**, 57), and Rundle and Sturdivant (*J. Amer. Chem. Soc.*, 1947, **69**, 1561), some of whose results are referred to below.

Although the trimethylplatinum derivatives are among the most stable of organometallic compounds, the study of organoplatinum compounds in general has received but scant attention. The preparation of anhydrous platinum tetrachloride, which has hitherto been used as a source of trimethylplatinum compounds, involves a somewhat laborious procedure for the thermal decomposition of chloroplatinic acid (*Inorg. Synth.*, Vol. II, p. 253), and our first problem was to find a more convenient starting material. The success experienced with pyridinotri-

chlorogold as a source of dialkylgold compounds (Gibson *et al.*, *J.*, 1935, 219 *et seq.*) prompted us to investigate the use of *cis*- or *trans*-dipyridinotetrachloroplatinum. The former separates almost quantitatively when sodium chloroplatinate is refluxed with the requisite quantity of pyridine in aqueous solution (Jörgensen, *Z. anorg. Chem.*, 1900, **25**, 369). The latter is obtained by oxidation of tetrapyridinoplatinous chloride $[py_4Pt]Cl_2$, which is itself readily prepared from potassium chloroplatinite (Jörgensen, *J. pr. Chem.*, 1886, [ii], **33**, 504).

It may be said at once that with the *trans*-isomer and methylmagnesium iodide very little, if any, alkylation occurred, the main product being dipyridinodi-iodoplatinum, presumably in the *trans*-modification. Certainly there was no indication of any trimethylplatinum compound.

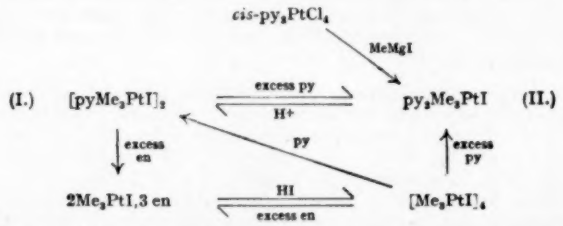
The *cis*-isomer, suspended in an anhydrous mixture of benzene and ether reacted completely with the Grignard reagent in 2 hours at 0—15°, giving, in 70% yield, a compound having an empirical formula $pyMe_3PtI$. The molecular weight, determined cryoscopically in benzene, showed clearly that the compound is binuclear and, without for the moment any attempt being made to elaborate the stereochemical configuration, may thus be represented by (I). The preservation of the characteristic 6-covalency of quadrivalent platinum (Lile and Menzies, *J.*, 1949, 1168; 1950, 617) by the halogen bridge is fully in keeping with the known structure of tetrameric trimethylplatinum chloride (Rundle and Sturdivant, *loc. cit.*) in which the same type of bridging occurs.

Dipyridinohexamethyl-$\mu\mu'$-di-iododiplatinum (I) is sparingly soluble in water, alcohol, ether, or acetone but soluble in chloroform or benzene. It is stable in dilute acid or alkaline solution, but decomposes in hot alkali, liberating pyridine. With further pyridine it is converted into dipyridinotrimethyliodoplatinum $Me_3Pt\,py_2I$ (II), identical with the complex prepared directly from trimethylplatinum iodide and excess of pyridine (Lile and Menzies, *loc. cit.*). The variation of freezing point depression of (II) in benzene, with concentration, indicated a dissociation in dilute solution: the apparent molecular weight (340) at infinite dilution is almost exactly two-thirds of the formula weight (525); at high concentrations the value approaches 525 (cf. p. 302). These observations may be interpreted in terms of the equilibrium:

$$2py + pyMe_3Pt\begin{matrix}\nearrow I \searrow \\ \searrow I \nearrow\end{matrix}PtMe_3py \rightleftharpoons 2py_2Me_3PtI$$
(I.) (II.)

Shaking a benzene solution of (II) with dilute hydrochloric acid removes one molecule of co-ordinated pyridine, with regeneration of the dimer (I).

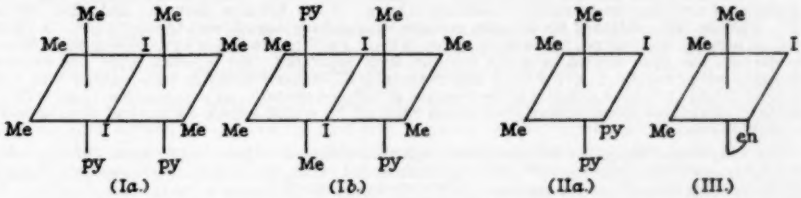
The stability of the dimer in dilute acid indicates that the second molecule of pyridine is held very much more firmly, but it may be displaced by addition of ethylenediamine to a chloroform solution of (I). The compound $2Me_3PtI,3en$, named by Lile and Menzies (*loc. cit.*) sesquiethylenediaminotrimethylplatinic iodide, separates as colourless crystals almost quantitatively. It has now been shown that by addition of hydriodic acid to a hot aqueous solution of this ethylenediamine complex, trimethylplatinum iodide $(Me_3PtI)_4$ may be obtained in good yield. The latter has in turn been converted into the dimer (I) by reaction with one equivalent of pyridine. These reactions are summarised in the scheme.



The constitutions of the various co-ordination complexes cannot be settled finally, but it is possible to make certain predictions.

In the tetramer trimethylplatinum chloride the three methyl groups attached to each platinum are *cis* to one another, *i.e.*, the three Pt–C bonds are mutually perpendicular. Assuming that trimethylplatinum iodide has a similar structure—and the molecular weight evidence of

Menzies and Overton (*J.*, 1933, 1291) would seem to confirm this—it is clear that formation of a co-ordination complex must involve a progressive splitting of the Pt–halogen links in the tetramer. That being so, co-ordination by one molecule of a monoamine, such as pyridine or ammonia, to each platinum will result in a dimer such as (I*a*), in which the four-membered ring is one face of the original cubic tetramer.

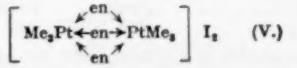


(Ia.) (Ib.) (IIa.) (III.)

Co-ordination of two molecules of a monoamine or one molecule of a diamine will give rise to a monomeric complex, as in (II*a*) or (III). The former is thus the most probable constitution of dipyridineiodotrimethylplatinum, and the latter that of Lile and Menzies's compound $Me_3Pt\,enI$.

In the sesquiethylenediamine compound, the process has been continued still further with the rupture of the sole remaining Pt–I bond, so that a salt is formed, of which the cation contains two platinum atoms bridged by at least one molecule of ethylenediamine, as for instance in (IV). The formula (V) suggested by Lile and Menzies cannot be ruled out on the evidence available, although our experience in the dialkylgold series (Foss and Gibson, *J.*, 1949, 3063) suggests that wherever possible ethylenediamine will chelate.

(IV.) $[en\,Me_3Pt{\leftarrow}en{\rightarrow}PtMe_3\,en]I_2$



I_2 (V.)

In *cis*-dipyridinotetrachloroplatinum, three methyl groups replacing three chlorine atoms may assume a mutually *cis*-position; this is not possible with the *trans*-isomer unless replacement is accompanied by reorientation of the groups attached to the platinum. The inability to isolate any trimethylplatinum compound from the *trans*-isomer, combined with the exceptionally high yield of pure compound prepared from the *cis*-isomer, seems to rule out the possibility of reorientation, and supports a mutually *cis*-arrangement of the methyl groups in these trimethylplatinum compounds.

cis-Dipyridinotetrachloroplatinum thus reacts with methylmagnesium iodide to give first *cis*-dipyridinoiodotrimethylplatinum (II*a*), which in the presence of acid loses one molecule of pyridine and dimerises, to give dipyridinohexamethyl-$\mu\mu'$-di-iododiplatinum. Either (I*a*) or (I*b*) may result from the dimerisation, but only one compound has been isolated in practice. That this compound proves to be identical with that obtained from trimethylplatinum iodide and one equivalent of pyridine favours the structure (I*a*).

Finally, it is interesting to compare the stability of the halogen bridge in the dimer (I), and in the parent trimethylplatinum halides too, with the weakness of the bridge in the recently described binuclear platinic complex, hexachlorobis(tri-*n*-propylphosphine)-$\mu\mu'$-dichlorodiplatinum (Chatt, *J.*, 1950, 2301).

Experimental.

cis-*Dipyridinotetrachloroplatinum.*—A mixture of sodium chloroplatinate (28·4 g.) and pyridine (8 g.) was refluxed in water (1·5 l.) for 16 hours. The yellow compound which separated was collected, washed with water, and dried *in vacuo*, first over calcium chloride and then over phosphoric oxide (yield 24 g., 95%) (Found: Pt, 39·5. Calc. for $C_{10}H_{10}N_2Cl_4Pt$: Pt, 39·4%).

cis-*Dipyridinodichloroplatinum.*—Pyridine (9·5 g.) was added to a solution of potassium chloroplatinite (25 g.) in water (300 c.c.), and the mixture was kept for 24 hours. The pale yellow solid which separated, was collected, washed with water and dried (yield 24 g., 94%).

Tetrapyridinoplatinous Chloride ($py_4PtCl_2,3H_2O$).—The preceding compound (24 g.) was dissolved in 50% aqueous pyridine (50 c.c.) on a water-bath. On the addition of ethanol (600 c.c.) and ether (3 l.) to the cold aqueous solution, the hydrated tetrapyridine salt separated as a white crystalline powder, which was collected, washed with ether, and air-dried. The yield was 34·5 g. (97%).

trans-*Dipyridinotetrachloroplatinum.*—Finely powdered potassium permanganate (12·4 g.) was added to a solution of the previous compound (30 g.) in concentrated hydrochloric acid (180 c.c.). The oxidation was allowed to proceed overnight, a further quantity of hydrochloric acid (300 c.c.) and then water (300 c.c.) were added, and the mixture was heated with stirring for 5 hours. The yellow amorphous solid which separated was collected, washed with water, and dried (yield 23 g., 93%) (Found: Pt, 39·0%).

Dipyridinohexamethyl-μμ′-di-iododiplatinum (I).—A solution of methylmagnesium iodide (6 mols.; from 3·7 g. of magnesium, 21·6 g. of methyl iodide, and 50 c.c. of ether) was run into a well stirred suspension of *cis*-dipyridinotetrachloroplatinum (12·4 g.) in dry benzene (200 c.c.) and ether (60 c.c.) at 0°. Stirring was continued for 2 hours, and the temperature was allowed to rise to 15°. A further 50 c.c. of benzene were added, followed by water (200 c.c.) and concentrated hydrochloric acid (50 c.c.). The mixture was then filtered, and the benzene layer separated; the aqueous layer was extracted thoroughly with benzene (2 × 100 c.c.), and the combined benzene solutions were washed with water and dried (Na_2SO_4). After removal of the benzene at reduced pressure, an orange-coloured solid (9·6 g.) remained. This was recrystallised from warm benzene, to which a little ligroin had been added to aid crystallisation.

Dipyridinohexamethyl-μμ′-di-iododiplatinum was thus obtained as pale yellow prisms (7·7 g., 70%), which decomposed slowly above 150° and completely at 217°. The platinum content was determined by carefully igniting the solid, in the presence of a few drops of chloroform and a few crystals of iodine. The molecular weight, determined cryoscopically in benzene, showed the complex to be binuclear (Found: C, 21·5; H, 2·9; N, 3·6; Pt, 43·7%; *M*, 891, 894. $C_{16}H_{28}N_2I_2Pt_2$ requires C, 21·5; H, 3·1; N, 3·1; Pt, 43·7%; *M*, 892). The compound is sparingly soluble in water, alcohol, and ether, soluble in chloroform and benzene, and very soluble in pyridine.

Dipyridinotrimethyliodoplatinum (II).—A solution of the preceding compound (3 g.) in pyridine (10 c.c.) was evaporated to dryness *in vacuo* over phosphoric oxide. The residue, when recrystallised from methanol, gave pale yellow crystals of dipyridinotrimethyliodoplatinum (2·4 g.) which melted at 168° (without decomp.), not depressed when mixed with Lile and Menzies's compound (personal communication) (Found: C, 29·9; H, 3·7; Pt, 37·1. Calc. for $C_{13}H_{18}N_2IPt$: C, 29·7; H, 3·6; Pt, 37·1%). The compound is sparingly soluble in water and cold alcohol, but dissolves readily in benzene, chloroform, acetone, and hot alcohol.

The table below shows the values of the observed freezing point depressions (Δt) and of the apparent molecular weight (M) at a series of concentrations (C; g. of solute/1000 g. of solvent):

C	3·85	8·92	13·68	18·07	24·2	29·03
Δt	0·050°	0·113°	0·160°	0·195°	0·250°	0·258°
M	369	413	447	485	507	527

By extrapolation of a derived graph, the apparent molecular weight at infinite dilution is found to be 340.

A benzene solution of dipyridinotrimethyliodoplatinum (0·5 g.) was shaken with dilute hydrochloric acid (25 ml.: 0·4N.). The benzene layer was then separated, dried (Na_2SO_4), and evaporated, to give pure dipyridinohexamothyl-μμ′-di-iododiplatinum (0·39 g., 92%), m. p. 216° (decomp.).

Sesquiethylenediaminotrimethylplatinic Iodide.—When ethylenediamine (0·1 g.) was added to a solution of dipyridinohexamethyl-μμ′-di-iodoplatinum (0·5 g.) in chloroform (20 c.c.), and the mixture warmed for a few minutes on a water-bath, colourless crystals of sesquiethylenediaminotrimethylplatinic iodide (0·50 g.) separated. The compound was water-soluble, darkened above 240° and melted with decomposition at 269° (cf. Lile and Menzies) (Found: Pt, 42·2. Calc. for $C_{15}H_{42}N_6I_2Pt_2$: Pt, 42·7%). The aqueous solution with silver nitrate gave an immediate precipitate of silver iodide.

Trimethylplatinum Iodide.—A hot aqueous solution of sesquiethylenediaminotrimethylplatinic iodide (0·62 g.) was treated with hydriodic acid (0·6 ml.; 7·3N.). The pale yellow solid which separated (0·46 g.) was collected, dried, and recrystallised from chloroform (Found: Pt, 52·5. Calc. for $C_{12}H_{36}Pt_4I_4$: Pt, 53·1%). When a chloroform solution (5 ml.) of trimethylplatinum iodide (0·1 g.), to which one equivalent (0·02 ml.) of pyridine had been added, was evaporated to a small bulk (approx. 1 ml.), crystals of dipyridinohexamethyl-μμ′-di-iododiplatinum (0·07 g.) separated; they had m. p. 215° (decomp.), undepressed when mixed with an authentic specimen.

Reaction of trans-*Dipyridinotetrachloroplatinum with Methylmagnesium Iodide.*—A solution of methylmagnesium iodide (Mg, 1·85 g.; MeI, 10·8 g.; Et_2O, 25 c.c.) was run into a well-stirred suspension of *trans*-dipyridinotetrachloroplatinum (6·2 g.) in dry benzene (100 c.c.) and dry ether (30 c.c.) at 0°. Stirring was continued for 2 hours, and the temperature was allowed to rise to 15°. As the reaction proceeded, the suspended solid became chocolate-brown. A further 50 c.c. of benzene were added, followed by water (100 c.c.) and concentrated hydrochloric acid (20 c.c.). The mixture was then filtered, and the solid collected was washed thoroughly with water and benzene. The dry substance (7·6 g.) was a dark brown amorphous powder, very sparingly soluble in all solvents except hot nitrobenzene from which separated on cooling, golden-yellow needles (3·7 g.) of dipyridinodi-iodoplatinum (Found: Pt, 32·4. Calc. for $C_{10}H_{10}N_2I_2Pt$: Pt, 32·1%). From the benzene layer of the filtrate was isolated only a small quantity (0·5 g.) of orange-coloured solid which has not been characterised.

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Department of Biochemistry and Chemistry,
Guy's Hospital Medical School, London, S.E.1. [*Received, September 28th*, 1950.]

68. *The Oxidation of Diphenylamine and of its N-Derivatives. Part II. Oxidation of the Benzyl Group of Some Benzylamines and Benzyl Ethers to Benzoyl.*

By James Forrest, S. Horwood Tucker, and (Miss) Margaret Whalley.

Oxidation, by means of potassium permanganate in acetone, of several benzyldiphenylamines, the dibenzyltoluidines, and tribenzylamine, and of benzyl ethers, gives the corresponding benzoyl derivatives.

Forrest, Liddell, and Tucker (*J.*, 1946, 454) showed that treatment of *N*-ethyldiphenylamine and of certain of its broom- and nitro-derivatives with potassium permanganate in acetone gives acetodiphenylamides, whilst benzyldiphenylamine yields benzodiphenylamide. Various other diphenylamines either did not react or gave tetraphenylhydrazine.

A number of tertiary amines, $X{\cdot}C_6H_4{\cdot}CH_2{\cdot}NRR'$, containing a benzyl (or substituted benzyl) radical, have now been prepared by heating a secondary or primary amine with benzyl (or substituted benzyl) chloride (A) alone, (B) in the presence of anhydrous potassium carbonate, or (C) in the presence of anhydrous sodium acetate. The addition, in the third method, (C), of a small amount of iodine appeared to have no beneficial effect (cf. Desai, *J. Ind. Inst. Sci.*, 1924, **7**, 235; *Chem. Abstr.*, 1925, **19**, 2645). These tertiary benzylamines were oxidised to the corresponding benzoyl derivatives by potassium permanganate in (*a*) acetone, (*b*) acetone–pyridine, or (*c*) acetone–pyridine–water. Method (*c*) seems to be the best, but it was not used until the work using method (*a*) was nearly complete. Where (*c*) was used it is particularly mentioned. In Table I the yields mentioned are not strictly comparable since, apart from the difference in the method of oxidation, ease of separation of the product from unchanged starting material varied, of course, from case to case.

Table I.

$X{\cdot}C_6H_4{\cdot}CH_2{\cdot}NRR' \longrightarrow X{\cdot}C_6H_4{\cdot}CO{\cdot}NRR'$.

	Benzyl derivative.	Benzoyl derivative, yield (method).
1.	*N*-*p*-Nitrobenzyldiphenylamine	70 (*a*)
2.	*N*-*p*-Bromobenzyldiphenylamine	91 (*b*)
3.	*N*-Benzyl-*N*-*p*-nitrobenzylaniline	30 (*c*)
4.	*NN*-Dibenzylaniline	38 (*a*)
5.	*NN*-Dibenzyl-*p*-anisidine	0 (*a*)
6.	*NN*-Dibenzyl-*o*-, -*m*-, and -*p*-toluidine	31, 19, 46 resp. (*a*)
7.	Tribenzylamine	20 (*a*)

N-Benzyl-*N*-methyl- and *N*-benzyl-*N*-ethyl-aniline gave inconclusive results [Method (*a*)].

It is clear that the presence of a *p*-bromo- or a *p*-nitro-group in the benzyl group greatly facilitates oxidation to the corresponding *p*-bromo- or *p*-nitro-benzoyl derivative.

It is noteworthy that in all these oxidations only monobenzoyl derivatives could be isolated, even from di- and tri-benzylamines (Nos. 6 and 7). The contrast between the results under Nos. 4 and 5 is striking.

The constitution of each of the three *N*-benzylbenzotoluidides was established by the synthetic sequence: toluidine ⟶ benzenesulphontoluidide ⟶ *N*-benzylbenzenesulphontoluidide ⟶ *N*-benzyltoluidine ⟶ *N*-benzylbenzotoluidide.

The well-known similarity in behaviour of many nitrogen and oxygen compounds prompted investigation of the oxidation of benzyl ethers by the above methods. Benzyl and substituted benzyl ethers proved somewhat more resistant to oxidation, but gave results comparable with the above. Thus, benzyl phenyl ether by method (*a*) or (*c*) gave a very small yield of phenyl benzoate. Since isolation of this small amount was very difficult, its presence was proved by

Table II.

$X{\cdot}C_6H_4{\cdot}O{\cdot}CH_2Ph \longrightarrow X{\cdot}C_6H_4{\cdot}O{\cdot}COPh$.

Ether.	Benzoate.	Yield, %.
Benzyl phenyl	Phenyl benzoate	*ca.* 2
p-Bromobenzyl phenyl	Phenyl *p*-bromobenzoate	>26 *
p-Nitrobenzyl phenyl	Phenyl *p*-nitrobenzoate	50
o-Methoxyphenyl *p*-nitrobenzyl	*o*-Methoxyphenyl *p*-nitrobenzoate	10
p-Methoxyphenyl *p*-nitrobenzyl	*p*-Methoxyphenyl *p*-nitrobenzoate	26

* Assessed as *p*-bromobenzoic acid.

alkaline hydrolysis to the acid. Again, the *p*-bromo- and *p*-nitro-benzyl phenyl ethers readily gave the corresponding phenyl *p*-bromo- and *p*-nitro-benzoates, which also were identified by hydrolysis. The *o*- and *p*-methoxyphenyl *p*-nitrobenzyl ethers gave the corresponding benzoyl derivatives in good yield. In Table II, yields are those obtained by oxidation method (*c*), which were invariably higher than those obtained by method (*a*) or (*b*).

Treatment of benzyl phenyl ether with potassium permanganate in aqueous phosphoric acid failed to give an oxidation product (cf. Schmidt and Nieswandt, *Chem. Ber.*, 1949, **82**, 1—oxidation of ·O·CH_2·O· to ·O·CO·O·).

Experimental.

The following descriptions of methods of preparing the required tertiary amines serve to illustrate the procedures adopted. Method (A) has already been described (Forrest, Liddell, and Tucker, *loc. cit.*).

N-p-*Bromobenzyldiphenylamine.*—*Method* (B). Diphenylamine (6 g., 1 mol.), *p*-bromobenzyl bromide (Weizmann and Patai, *J. Amer. Chem. Soc.*, 1946, **68**, 150) (6·3 g., 1 mol.), and anhydrous potassium carbonate (4·5 g., 1·3 mols.) were heated together at 175° (in a flask connected to a eudiometer) until no more carbon dioxide was evolved (2·5 hours). The reaction mixture was treated with water and extracted with ether, the ether removed, and the semi-solid residue washed with 70% (v/v) aqueous ethanol to remove unchanged diphenylamine. Crystallisation from ethanol gave sword-blade crystals of N-p-*bromobenzyldiphenylamine*, m. p. 83—84° (4·6 g., 55%) (Found: C, 67·3; H, 4·7. $C_{19}H_{16}NBr$ requires C, 67·45; H, 4·7%).

Method (C), *Desai's modification* (loc. cit.). Diphenylamine (4·2 g.), *p*-bromobenzyl bromide (6·3 g.), anhydrous sodium acetate (2 g.), and iodine (0·02 g.) gave *N*-*p*-bromobenzyldiphenylamine (4·7 g., 56%). Generally, the addition of iodine in similar preparations appeared to have no effect. *N*-*p*-Bromobenzyldiphenylamine became bluish-green in air, but remained colourless in a sealed glass tube.

N-p-*Nitrobenzyldiphenylamine.* Method (*B*), carried out at 155° for 3 hours, gave lustrous plates (from light petroleum, b. p. 60—80°; then methanol), m. p. 92—94° (51%) [Desai, *loc. cit.*, claimed a 70% yield of a compound insoluble in light petroleum, with m. p. 93·5°. Using his method, we confirmed our results (52%). Lyons, *J. Amer. Pharm. Assoc.*, 1932, **21**, 224, gives m. p. 96°].

N-*Benzyl*-N-p-*nitrobenzylaniline.*—*Method* (B). *N*-Benzylaniline (1 mol.), *p*-nitrobenzyl chloride (1·1 mols.), and anhydrous potassium carbonate (2 mols.) were heated at 150° for 3—4 hours, the mass was then treated with water, and the insoluble solid crystallised (from acetic acid, then ethyl acetate) as lemon-yellow needles, m. p. 143—144° (70%) (Found: C, 75·6; H, 5·9; N, 8·9. $C_{20}H_{18}O_2N_2$ requires C, 75·5; H, 5·7; N, 8·9%).

N-*Benzyl*-N-*ethylaniline picrate* formed lemon-yellow, hexagonal prisms (from benzene), m. p. 126—128°, softening at 120° (Found: C, 57·1; H, 4·4; N, 12·6. $C_{13}H_{17}N,C_6H_3O_7N_3$ requires C, 57·3; H, 4·5; N, 12·7%).

Benzamides.—(A) *By oxidation.* (i) *Method* (a) (Forrest, Liddell, and Tucker, *loc. cit.*). The following were thus obtained: *p*-nitrobenzodiphenylamide, pale yellow prisms (from ethanol), m. p. 152—154° (70%) (Chapman, *J.*, 1927, 1749, gives m. p. 156—157°) (Found: C, 72·0; H, 4·6; N, 9·0. Calc. for $C_{19}H_{14}O_3N_2$: C, 71·7; H, 4·4; N, 8·8%); *N*-benzylbenzanilide, m. p. 103—104° (38%); *N*-*benzylbenzo*-*o*-*toluidide*, prisms (from light petroleum, b. p. 40—60°), m. p. 65—67° (31%) (Found: C, 82·2, 82·2, 82·4; H, 6·3, 6·3, 6·6; N, 4·5. $C_{21}H_{19}ON$ requires C, 83·7; H, 6·3; N, 4·7%); *N*-benzylbenzo-*m*-toluidide, stout prisms (from light petroleum, b. p. 60—80°), m. p. 70—71° (19%) (Grunfeld, *Bull. Soc. chim.*, 1937, [v], **4**, 654, gives m. p. 69°) (Found: C, 83·8; H, 6·3; N, 4·6%); *N*-benzylbenzo-*p*-toluidide, stout prisms (from methanol), m. p. 124—125° (46%) (Found: C, 83·85; H, 6·5; N, 4·7%) (Rabaut, *Bull. Soc. chim.*, 1891, [iii], **6**, 139, found m. p. 87—88°). Tribenzylamine on oxidation gave *NN*-dibenzylbenzamide (20%).

(ii) *Method* (b). This is exemplified by the following. *N*-*p*-Bromobenzyldiphenylamine (1 g.) in acetone (20 ml.) and pyridine (2 ml.) was treated with finely-powdered potassium permanganate (2·5 g.) portionwise, the mixture being boiled after each addition until the permanganate colour nearly vanished (45 minutes in all). The stirred mixture was boiled for an hour and then treated with a solution of sodium pyrosulphite in dilute sulphuric acid, and the product crystallised from methanol to give faintly yellow sword-blade prisms, m. p. 143—145° (0·95 g., 91%), of p-*bromobenzodiphenylamide* (Found: C, 65·0; H, 4·3; N, 4·2; Br, 23·3. $C_{19}H_{14}ONBr$ requires C, 64·8; H, 4·0; N, 4·0; Br, 22·7%). This was boiled with ethanolic potassium hydroxide for 0·5 hour, water was added, and the solution extracted with ether. The aqueous fraction on treatment with hydrochloric acid gave a pale bluish solid which crystallised from acetic acid in rectangular laminæ, m. p. 248—249°, undepressed on admixture with *p*-bromobenzoic acid (Found: C, 41·9; H, 2·5. Calc. for $C_7H_5O_2Br$: C, 41·8; H, 2·5%).

(iii) *Method* (c). This is exemplified by the following. *N*-Benzyl-*N*-*p*-nitrobenzylaniline (0·5 g.), acetone (10 ml.), pyridine (0·2 ml.), water (0·2 ml.), and potassium permanganate (0·5 g., added all at once) were boiled together for 20 minutes, and the product was worked up as above. Unchanged material (0·07 g.) was left as yellow needles when the precipitated oxidation product was boiled with methanol; the evaporated extract, recrystallised from benzene–light petroleum (b. p. 60—80°), gave N-*benzyl*-p-*nitrobenzanilide*, m. p. 120—122° (0·16 g., 30%) (Found: C, 72·3; H, 5·0; N, 8·3. $C_{20}H_{16}O_3N_2$ requires C, 72·3; H, 4·8; N, 8·4%).

(B) *By benzoylation.* This provided specimens for comparison. *E.g.*, *p*-bromobenzoic acid (5 g.) was heated on a water-bath with phosphorus pentachloride (1·7 g.) for 3·5 hours: a solution of diphenylamine (4·2 g.) in pyridine (10 ml.) was added and the mixture heated for 0·5 hour. The pyridine was

removed under reduced pressure, and the residue acidified with 20% hydrochloric acid to give pale yellow prisms (from methanol) (6·0 g., 57%), m. p. 143—145°, alone or on admixture with the product obtained by oxidation. Standard methods gave *N-methyl-*, faintly brown plates [from benzene–light petroleum (b. p. 60—80°)], m. p. 103—106° (Found: C, 65·6; H, 4·8; N, 11·1. $C_{14}H_{13}O_3N_3$ requires C, 65·6; H, 4·7; N, 10·9%), and *N*-ethyl-*p*-nitrobenzanilide, pale brown, diamond-shaped crystals [from benzene–light petroleum (b. p. 60—80°)], m. p. 115—117° (softening at 111°) (Lockemann, *Ber.*, 1942, **75**, 1917, found m. p. 119—120°) (Found: C, 67·0; H, 5·2; N, 10·4. Calc. for $C_{15}H_{14}O_3N_2$: C, 66·7; H, 5·2; N, 10·4%). The action of *p*-nitrobenzoyl chloride on *N*-benzylaniline gave *N*-benzyl-*p*-nitrobenzanilide, m. p., alone or on admixture with the compound prepared as above by the oxidation of *N*-benzyl-*N*-*p*-nitrobenzylaniline, 120—122°.

Syntheses of N-*Benzylbenzotoluidides.*—The *N*-benzenesulphontoluidide (10 g.) was dissolved in the theoretical amount of N-sodium hydroxide, and the calculated amount of benzyl chloride (redistilled in a vacuum) was added slowly to the stirred solution, at 40—45° during 1·5 hours; ethanol (50 ml.) was then introduced, and the mixture refluxed (1·5 hours). The oil which separated crystallised slowly on cooling, and was recrystallised from ethanol. Thus were obtained *N-benzylbenzenesulphon-o-*, needles, m. p. 107—109° (8·0 g., 58%) (Found: C, 71·2; H, 5·6. $C_{20}H_{19}O_2NS$ requires C, 71·2; H, 5·7; N, 4·15%), *-m-*, needles, m. p. 102—105° (4·5 g., 32%) (Found: C, 71·2; H, 5·6%), and *p*-toluidide, prisms, m. p. 121—122° (8 g., 58%) (Apitzsch, *Ber.*, 1900, **33**, 3524, gives m. p. 123—124°) (Found: C, 71·5; H, 5·8; N, 4·3%).

The *N*-benzylbenzenesulphontoluidide (2 g.) was warmed with 60% sulphuric acid (2 ml.) at 125° for 1 hour (cf. Apitzsch, *loc. cit.*). The solution was poured into water, filtered, and basified with sodium hydroxide solution. The oil which separated was shaken with benzoyl chloride and sodium hydroxide solution, giving *N*-benzylbenzo-*o-* (0·1 g., 5%), *-m-* (0·4 g., 20%), and *-p*-toluidide (0·15 g., 8%).

Benzyl Ethers and Their Oxidation Products.—The benzyl ethers were prepared by interaction of the appropriate benzyl chloride or bromide and the sodium phenoxide (cf. Powell and Adams, *J. Amer. Chem. Soc.*, 1920, **42**, 657). Benzyl *o*-methoxyphenyl ether had m. p. 57—58° (Claisen, *Annalen*, 1925, **442**, 244, gives m. p. 62°, and Birch, *J.*, 1947, 104, m. p. 58—59°); the *p*-isomer had m. p. 66—68° (cf. Smith, *J.*, 1931, 256). The following are new: *methyl* m-*benzyloxybenzoate*, stout prisms (from ethanol), m. p. 68—70° (Found: C, 74·6; H, 5·8. $C_{15}H_{14}O_3$ requires C, 74·4; H, 5·8%), and the p-*isomer* (from ethanol), m. p. 98—100° (Found: C, 74·2; H, 5·7%); *o-methoxyphenyl* p-*nitrobenzyl ether*, pale brown prisms (from methanol), m. p. 64—65° (Found: C, 65·1; H, 5·3; N, 5·5. $C_{14}H_{13}O_4N$ requires C, 64·9; H, 5·05; N, 5·4%), and its p-*isomer*, pale yellow prisms (from methanol), m. p. 86—88° (Found: C, 65·0; H, 5·1; N, 5·4%).

Oxidation was by the standard procedures adopted for the oxidation of the amines; but the best results were obtained by using the ether (0·5 g.), acetone (10 ml.), pyridine (0·2—0·5 ml.), water (0·2—0·5 ml.), and potassium permanganate (0·5—1·0 g., added all at once), boiling being continued for 2—5 hours until practically all permanganate colour had disappeared. Thus benzyl phenyl ether gave, after removal of unchanged ether by repeated crystallisation from methanol and finally from light petroleum (b. p. 40—60°), stout rods, m. p. 67—68°, of phenyl benzoate (1—2%). Since this could not be invariably repeated, the residue obtained after removal of most of the unaltered ether was hydrolysed by boiling it with sodium hydroxide (0·1 g.) in ethanol (5 ml.) for 1 hour, and worked up in the usual way to give benzoic acid, m. p. and mixed m. p. 120—122°. Similarly, *p*-nitrobenzyl phenyl ether, by the above modified method (2·25 hours), gave, after the usual treatment with sulphurous acid solution, phenyl *p*-nitrobenzoate, m. p. 125—127° (from methanol) (50%); this was hydrolysed to *p*-nitrobenzoic acid, m. p. 235° (lit., 242°). *p*-Bromobenzyl phenyl ether similarly gave phenyl *p*-bromobenzoate—not isolated, but hydrolysed to *p*-bromobenzoic acid (26%), m. p. and mixed m. p. 248° (lit., 251°). *o*-Methoxyphenyl *p*-nitrobenzyl ether on oxidation gave faintly green material, which by fractional crystallisation from methanol gave starting material and *o-methoxyphenyl* p-*nitrobenzoate* (10%), m. p. 102—104° (Found: C, 61·4; H, 4·2; N, 5·0. $C_{14}H_{11}O_5N$ requires C, 61·5; H, 4·1; N, 5·1%). Similarly was obtained p-*methoxyphenyl* p-*nitrobenzoate*, needles (from ethanol), m. p. 113—115° (26%) (Found: C, 61·9; H, 4·0; N, 4·5%); hydrolysis of the *o*-ester gave an unworkable black solution.

We are indebted to the Department of Scientific and Industrial Research for a Grant to one of us (M. W.), and to Mr. W. M. O. Rennie, B.Sc., for assistance; also to Mr. J. M. L. Cameron and to Miss R. H. Kennaway for microanalyses.

UNIVERSITY OF GLASGOW. [*Received, October 5th*, 1950.]

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69. *The Hydrogen–Calomel Cell. Part I. The Hydrogen Electrode.*

By G. J. HILLS and D. J. G. IVES.

Some errors to which the hydrogen electrode is susceptible are discussed. A new form of hydrogen electrode is described and some comments are made on the theory of operation of the hydrogen electrode.

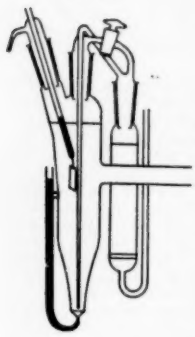
THE hydrogen–calomel cell, H_2,Pt|HCl(aq.)|Hg_2Cl_2|Hg, has not hitherto been used for electrochemical work of high precision, and its standard E.M.F. has not been directly determined.

This is because the calomel electrode has shown intractably erratic behaviour in dilute solutions and has therefore been discarded in favour of the silver/silver chloride electrode, with which nearly all the potentiometric work of general thermodynamic importance has been done. No good reasons have been advanced for the defects of the calomel electrode and it seemed desirable to try to remedy this situation because it was felt that, in fact, this electrode should be superior to its silver analogue. Any electrode in which the metal phase is the reduced form of the redox equilibrium system must vary in potential according to the state of the metal, which, in turn, will depend upon purity and thermal and mechanical history. The difficulties encountered with hard metals are by no means absent in the case of silver, but hardly arise with liquid mercury, which may be easily brought to a reproducible, standard state. Of all metals, therefore, mercury should be the most suitable for forming a truly reversible and reproducible electrode. Evidence will be given in the following papers that, in conformity with this view, the calomel electrode is superior to the silver/silver chloride electrode: means have been found to minimise the defects that have hitherto obscured this position and the hydrogen–calomel cell is suggested as being the most suitable for accurate thermodynamic work. In the course of this study it has been found necessary to devote some attention to the hydrogen electrode, to which all other measured electrode potentials are referred, and this forms the subject matter of Part I.

The Hydrogen Electrode.

It is common practice to use a number of hydrogen electrodes in the same half-cell, and interagreement is accepted as an indication that the true, reversible potential has been attained. Effective use of this criterion requires the individual electrodes to differ in type and preparation to minimise the possibility of common errors. Available hydrogen electrodes, however, vary but little: all in current use consist of catalytically active platinum electrodeposited on a noble-metal substrate, and it was therefore considered whether some wide deviation from the normal type might not be advantageous. The view was taken that the hydrogen electrode resembles oxidation-reduction electrodes (*e.g.*, $Pt|Fe^{2+},Fe^{3+}$) in that both oxidised and reduced forms (hydrogen ions and dissolved molecular hydrogen) are contained in the solution phase but differs in that, in the absence of catalyst, there is no free electron transfer either between the components in the solution or across the metal/solution interface. The one system could be brought closest in line with the other by dispersal of catalyst throughout the solution rather than by confining it to the interface, and this might facilitate general mobility in the redox equilibrium system. The argument is tenuous, but it was found that Biilman and Klit (*Z. physikal. Chem.*, 1927, **130**, 566) had already adopted the idea, and used a bright platinum or gold electrode immersed in a hydrogen-saturated solution to which a small amount of colloidal platinum had been added. The results were satisfactory, but the method does not lend itself to general application. It has been found, however, that a small quantity of dry platinum black may be added in place of the platinum sol and leads to an extremely satisfactory electrode, which will be called "the catalyst electrode." The requirements that (*a*) the heavy platinum black should be continuously dispersed throughout the half-cell solution, (*b*) it should come repeatedly into contact with the bright platinum electrode, and (*c*) it should be unable to collect in recesses undisturbed by circulating solution defined the physical design of the electrode. which is illustrated in Fig. 1. A normal hydrogen electrode included in the same vessel showed agreement in potential with the catalyst electrode to within 10 μv., and the two together furnished a hydrogen-electrode assembly, used in all subsequent measurements, admirably satisfying the criterion of validity previously mentioned. The catalyst electrode has some advantages. The apparatus is robust and can be cleaned and dried by the usual methods without special precautions. In operation, it is less prone to "fatigue" than the normal electrode. It may be significant (cf. Beans and Hammett, *J. Amer. Chem. Soc.*, 1925, **47**, 1215) that the catalyst electrode is free from the disadvantages associated with the electrodeposition of platinum from strongly acid solutions. It does not require special preparations before use, for a large stock of catalyst may be prepared at one time and stored in a dry state, a few mg. being required for each half-cell. The electrode approaches to within 100 μv. of its equilibium potential in a few minutes after the addition of catalyst and passage of hydrogen, and reaches

FIG. 1.



its final potential in about an hour. If, during this period, the bubbling of hydrogen is stopped, the potential drifts in a positive sense, but, when the catalyst is completely in equilibrium with hydrogen, this does not occur, and the hydrogen stream may be stopped (in practice, by-passed over the surface of the solution) for measurements to be made. Details of the construction of the electrode are given in the experimental section.

During the course of the work with hydrogen electrodes, a source of error was identified of which no mention can be found in the literature and on which a preliminary report has been made (Hills and Ives, *Nature*, 1949, **163**, 997). The potential of a normal hydrogen electrode is independent of its depth of immersion below the surface of the solution, since a reasonable bubbling rate of hydrogen ensures sufficient stirring to make the solution homogeneous with respect to dissolved hydrogen. The potential of the electrode, however, is dependent upon the depth at which hydrogen bubbles are delivered in the solution; because of the additional hydrostatic pressure within the gas bubbles, the solution becomes supersaturated with respect to the pressure of gas over the solution. It is therefore necessary to determine the pressure of hydrogen, in excess of atmospheric pressure, with which the solution is effectively in equilibrium, for it is this which is potential-determining and not the measured barometric pressure. It was found to be impracticable to solve this problem except by an empirical study. For this purpose a cell was set up consisting of two well-separated electrode compartments; one of these contained a normal hydrogen electrode supplied with hydrogen from a bubbler of fixed depth, the other also contained a normal hydrogen electrode but could be supplied with hydrogen either from a fixed jet at the bottom of the vessel, or, alternatively, from a jet of variable depth of immersion. The E.M.F. of this cell (ideally zero) varied according to the depth of delivery of hydrogen in the second half-cell; the behaviour was quite systematic, the E.M.F. responding rapidly when the hydrogen was diverted from one jet to the other. The results, for a cell containing N/10-hydrochloric acid, are shown in the table. The first column shows the difference in depth between the fixed and variable jets in the second half-cell; the second column shows the change in E.M.F. on passing from the lower, fixed bubbler to the upper, variable one and is compared in the third column with the change which would be expected if the full hydrostatic head of solution were operative. The last column gives the ratio of these quantities.

Change of bubbler depth, cm.	ΔE (obs.), μv.	ΔE (calc.), μv.	$\frac{\Delta E \text{ (obs.)}}{\Delta E \text{ (calc.)}}$
3·3	20	41	0·49
7·8	42	98	0·43
11·0	57	137	0·41
14·0	72	175	0·42
17·5	88	219	0·42

A plot of change of E.M.F. against change in bubbler depth is sensibly linear, and the slope of the best straight line gives a value, for what may be termed " the supersaturation factor," of $0{\cdot}42 \pm 0{\cdot}02$. This is the factor by which the depth of immersion of the hydrogen bubbler must be multiplied in order to obtain the effective excess of hydrostatic pressure. It must be applied as a correction to all hydrogen-electrode measurements in the course of adjusting the observed potentials to the standard hydrogen pressure of one atmosphere.

It might be expected that this factor would vary considerably according to the area of the upper free surface of the solution, in direct contact with hydrogen at atmospheric pressure. This appears not to be the case because of the very low rate of transfer of hydrogen across the free-surface interface as compared with the much greater rate of transfer across the interface of a rising bubble. This has been demonstrated in the following ways :

(*a*) A hydrogen half-cell was fitted with a restricted gas outlet and manometer, permitting hydrogen to be bubbled through the solution, or by-passed over its surface, at controlled pressures in excess of atmospheric. In a typical experiment of this kind, hydrogen was bubbled at an excess of pressure of 13·5 cm. of water and the electrode showed an enhanced (negative) potential of 160 μv., in reasonable agreement with the calculated increment (170 μv.). When the hydrogen stream was by-passed over the surface of the solution and the excess of pressure simultaneously released, the increment of potential remained unchanged for at least two hours. A similar experiment in which, on the release of excess of pressure, hydrogen at normal pressure was bubbled through the solution gave an entirely different result, the initial 160-μv. increment in potential falling almost immediately to zero. In a third experiment, an identical excess of pressure applied whilst hydrogen was by-passing over the surface of the solution produced no perceptible effect.

(*b*) A normal hydrogen half-cell was set up, with hydrogen bubbling through the solution. When a very rapid stream of pure nitrogen was passed directly over the free surface of the solution so as to render the partial pressure of hydrogen at the surface almost negligible, the electrode showed a positive increment of potential of only 2·7 mv. A very rough calculation on this basis indicated that the " hydrogen transfer efficiency " of the free surface is of the order of 4% of that of the rising bubble surface.

(*c*) In very many experiments it has been found that hydrogen-electrode potential is sensibly independent of the rate of bubbling; it is therefore also independent of the ratio of bubble surface area to free surface area, which can only be the case if the free surface is virtually ineffective in controlling the concentration of hydrogen in solution.

These experiments leave no doubt that it is the concentration of dissolved hydrogen which is potential-determining, and this concentration must therefore be controlled, in electrochemical work of high precision, with as great care as that of any other solute.

Errors can also readily arise by failure to attain or maintain the maximum concentration of dissolved hydrogen. This is likely to occur in ill-designed half-cells which contain stagnant regions of solution not swept out by bubbles of hydrogen, or when connection is opened between the hydrogen-electrode vessel and another half-cell. It has been found advisable, in this connection, to interpose a buffer compartment, containing a guard hydrogen electrode, between the two halves of, for example, the hydrogen–calomel cell.

Experimental.

Normal Hydrogen Electrodes.—Pieces of platinum or gold foil were welded to 28-S.W.G. platinum wires, which were sealed into soft-glass tubes mounted on *B*19 soft-glass cones. The electrodes were annealed in an alcohol flame and used as cathodes in the electrolysis of 2% platinic chloride solution in 2N-hydrochloric acid for 10—20 minutes (2 v.; 10—20 ma./cm.^{2}). The resulting, lightly platinised electrodes were dark grey with the original metal sheen clearly visible. They were washed well with water and kept in water when not in use. The use of lead acetate in the plating solution, and the alternating cathodic and anodic electrolyses both in the platinising solution and afterwards in dilute sulphuric acid (Popoff, Kunz, and Snow, *J. Physical Chem.*, 1928, **32**, 1056) were not found to be beneficial and were discarded.

The Catalyst Electrode.—The conditions necessary for the proper operation of this electrode could only be met by arranging a conical electrode of bright platinum foil at the base of the electrode vessel, the hydrogen stream being delivered close to the apex of the cone so as to lift the catalyst continually into suspension. Since it was necessary to make the electrode vessel of Pyrex glass and to avoid any crevices in the construction where catalyst might collect and be occluded, latitude in design was small. Constructions involving seals of platinum wire through Pyrex were unsatisfactory; apart from tendencies to leak or crack, the potentials recorded at such electrodes were very erratic. It has been pointed out that such misbehaviour may arise from strain effects at metal/glass/solution junctions (Garrett, Hogge, and Huikes, *Science*, 1940, **92**, 18), and it is believed that this is the case. The difficulty was obviated by using very thin, light, glass construction and extremely thin platinum foil (0·0004"), a narrow strip of which may be " pinch-sealed " into Pyrex glass to give a vacuum-tight seal (Campbell, *J. Amer. Chem. Soc.*, 1929, **51**, 2419). A disc, 8 mm. in diameter, was punched from the platinum foil and a segment was cut out so as to allow of the formation of a cone. A narrow contact strip was cut along one of the edges left by removal of the segment and was bent down so as to be coaxial with the cone, which was shaped by hand. The resulting electrode was slipped into the thin-walled, conical base of the electrode vessel, the contact strip protruding into a small contact tube provided. The pinch seal was then made and the platinum cone sweated to its glass substrate, forming an assembly free from strain, leaks, and crevices.

Catalyst. A 2% solution of platinic chloride, containing 5% of sodium acetate, was shaken in an atmosphere of hydrogen until reduction was complete. The platinum black was filtered off, washed, repeatedly soaked in water, and finally dried in a vacuum.

Hydrogen. Cylinder hydrogen was purified by passage over platinised asbestos and reduced copper, heated in silica tubes at *ca.* 700°. Connections between the cylinder and the furnace tubes were made with polyvinyl chloride tubing, rubber being excluded. After purification, the gas passed through all-glass connections to presaturators mounted adjacent to the electrode vessels in the thermostat, which was maintained at 25° in all the experiments.

Hydrochloric acid. Hydrogen chloride, generated from " AnalaR " ammonium chloride, was dissolved in conductivity water, and the solution chlorinated and boiled to remove traces of other halogens. The acid was then fractionally distilled, and a constant-boiling fraction collected and stored in a quartz flask. This stock acid was diluted with conductivity water as necessary.

Potentiometric measurements. The apparatus and technique are fully described in Part III (*J.*, 1950, 318).

Discussion.

There is some difficulty in understanding the mechanism of the reversible hydrogen electrode. Whereas the discharge of hydrogen ions from solution normally requires an overpotential, it

occurs freely at a platinised-platinum surface without appreciable activation energy, and this is attributed to the heat of adsorption of hydrogen atoms on the catalytically active surface. But this very property of platinised platinum which facilitates discharge would appear to hinder the reverse process; yet the transition must be unhindered in either direction if the electrode is to operate reversibly. According to Butler (*Proc. Roy. Soc., A*, 1936, **157**, 423), a hydrogen atom (or ion) may occupy alternatively two potential-energy minima, one on each side of the transition process of charge or discharge. On the one hand, as a hydrogen ion, it may occupy the lowest vibrational level in a water molecule close to the metal surface; on the other hand, as an atom, it may occupy a position of minimum energy at an adsorption site on the platinum surface. The equilibrium potential is that at which these alternative minima are at approximately the same level on the energy scale and are separated from each other by a small barrier which allows the charge and discharge processes to occur at equal and appreciable rates.

There can be little doubt that this theory is substantially correct, but a difficulty remains in that the potential of the reversible hydrogen electrode must be uniquely defined by the thermodynamic relationship $2\mu_{H^+} - \mu_{H_2} - 2E\mathbf{F} = 0$, which does not allow of self-adjustment of potential to fit a possibly variable adsorption energy. This further difficulty may be obviated by the suggestion (Audubert, *Faraday Soc. Discussions*, 1947, **1**, 72) that charge and discharge do not necessarily occur at the same sites and are not necessarily strictly the reverse of each other. Any metal surface is inhomogeneous, containing sites for atoms, some occupied and some not, covering a range of energies. This must also be the case for adsorption sites on a metal surface, for which there will be a range of adsorption energies (indicated by decreasing differential heat of adsorption); only certain of the corresponding energy levels for adsorbed hydrogen atoms will be suitable for the charge and discharge processes of the hydrogen electrode. All those metals for which differential adsorption energies fall within the required range will operate as reversible hydrogen electrodes, showing potentials defined only by the thermodynamic equilibrium between hydrogen gas and solution ions, the function of the metal being solely to decapitate the barrier separating these two extreme states. Even within the limited range of suitable levels, it is likely that discharge occurs preferentially at sites of lower level, and charge at sites of higher level, a cyclic equilibrium being maintained by the ready redistribution of adsorbed hydrogen atoms which must occur. The Butler theory may then be modified by replacing a single potential-energy curve for a hydrogen atom under the influence of the surface by a band, spread over the relevant energy range: each process can then occur at the site best suited to it and no non-thermodynamic restriction is imposed on the potential of the electrode.

Differentiation between charge and discharge sites is indicated in studies of working hydrogen electrodes. Hammett (*J. Amer. Chem. Soc.*, 1924, **46**, 7) has made a careful study of "the velocity of the hydrogen electrode reaction" at various platinum electrodes under small anodic and somewhat larger cathodic polarisations. For a series of electrodes of varying catalytic activity, current, plotted against polarising potential, gave smooth curves passing through the origin without inflexion (cf. Dolin, Ershler, and Frumkin, *Acta physicochim. U.R.S.S.*, 1940, **13**, 779) which were shown (Hammett, *Trans. Faraday Soc.*, 1933, **29**, 770) to be accurately interpreted by the equations

$$I = -k_1 e^{-\mathbf{F}V/2\mathbf{R}T} + k_2[\mathrm{H}]e^{\mathbf{F}V/2\mathbf{R}T} \quad \ldots\ldots\ldots\ldots \quad (1)$$

$$\frac{d[\mathrm{H}]}{dt} = 0 = k_1 e^{-\mathbf{F}V/2\mathbf{R}T} - k_2[\mathrm{H}]e^{\mathbf{F}V/2\mathbf{R}T} + k_3[\mathrm{H_2}] - k_4[\mathrm{H}]^2 \quad \ldots\ldots \quad (2)$$

where I is the net current flowing at a polarisation V with respect to the reversible hydrogen electrode (cathodic current and potential being given negative sign), [H] is the particular surface activity of adsorbed hydrogen atoms on the electrode when the steady current appropriate to each polarisation is established, and the other symbols have their usual significance.

These results have been re-examined by using equation (1) modified to include the characteristic activation energies of discharge and charge processes (ω and ω', respectively) and the relevant energy-transfer factors, α and β, not necessarily equal to 0·5. For example, the gross discharge current is expressed by

$$I_{\text{discharge}} = -ke^{(\omega + \alpha\mathbf{F}V)/\mathbf{R}T} \quad \ldots\ldots\ldots\ldots \quad (3)$$

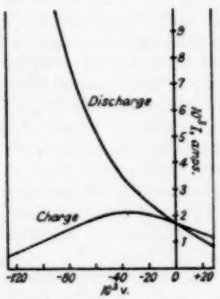
Plots of $\log_{10}(-I)$ against $(-V)$ for each of the four electrodes considered gave a series of curves asymptotic in the direction of increasing cathodic polarisation to parallel straight lines, the common slope of which gave a value of 0·50 for α and a Tafel "b value" of 0·118, consistent with well-established overvoltage results at unpoisoned platinum electrodes. On the assump-

tion that no change in mechanism of discharge occurred over the whole polarisation range (−0·1 to 0·02 v.), these straight lines were used to calculate the value of the gross discharge current for each polarisation, and, by subtraction from the known net current, the value of the gross charge current. A typical result is shown in Fig. 2, the main features of which require comment.

At the highest cathodic polarisation the charge current is surprisingly high, much greater than the discharge current under correspondingly unfavourable (anodic) polarisation. As the negative polarisation is reduced, discharge current of course decreases in the manner dictated by the initial assumption and, at first, charge current increases in the manner to be expected if the main rate-limiting step were $H \longrightarrow H^+ + e^-$. With further decrease in negative polarisation, however, the charge current passes through a flat maximum and thereafter decreases steadily, even when anodic polarisation supervenes. This can only be because the rate of provision of hydrogen atoms is becoming rate-limiting: as the charge process increases in facility, a major supply of hydrogen atoms, the discharge process, dwindles until eventually charging can only occur at the rate defined by the atomisation of molecular hydrogen. Intermediately, charging will take place with a velocity proportional to $[H]e^{-(\omega' - \beta FV)/RT}$, where [H] is defined by the resultant effect of the four processes indicated in equation (2).

At the equilibrium potential, $V = 0$, the exchange current, even with these comparatively inactive electrodes, is considerable. The discharge current, it is credibly assumed, is controlled solely by the step $H^+ + e^- \longrightarrow H$, but the equal and opposite charge current flows at a rate largely restricted by the supply of hydrogen atoms, as indicated by the slopes of the "charge curve" previously discussed, and is effectively unhindered by any barrier in the step $H \longrightarrow H^+ + e^-$. It follows that the activation energy for charge is smaller than that for discharge. Further, for all these differing electrodes which operate as reversible hydrogen electrodes, it is clear that the adsorbed hydrogen atoms must be in equilibrium with molecular hydrogen, so that the activity of hydrogen atoms on the electrode must be defined by the hydrogen gas pressure alone. This is also clear from the necessary equality, at equilibrium, of the third and fourth terms on the right-hand side of equation (2). The question then arises whether it is charge or discharge which is decisive in controlling the magnitude of the exchange current. It is unlikely that discharge is, over the small polarisation range involved, in any way dependent upon the population of hydrogen atoms on the electrode and may be assumed to occur at a rate defined, at $V = 0$, solely by the properties of a given electrode and of the solution with which it is in equilibrium. There will be variation from electrode to electrode, but for *all* electrodes that operate reversibly, the charge current must in each case come to the same value as the discharge current. There must therefore be some self-adjusting kinetic factor in the charge process and the non-exponential factors are excluded from this rôle by thermodynamic considerations. The evidence strongly favours the view that it is the activation energy of charging which is self-adjusting. The migration of hydrogen atoms to adsorption sites covering a range of higher energy levels seems to be the only way in which this could be so. The fact that in a number of cases, and perhaps in most, the activation energy for charge is less than that for discharge lends support to this view.

FIG. 2.



If it is accepted that the reversible hydrogen electrode operates by a cyclic process of the type envisaged, it is probable that at the catalyst electrode discharge of hydrogen ions occurs predominantly on the suspended platinum black, and charge of hydrogen atoms mainly at the platinum cone. The rapid circulation of catalyst, and its frequent and repeated contact with the cone, redistributes the hydrogen and brings the cone to the true equilibrium hydrogen electrode potential.

BIRKBECK COLLEGE, LONDON, E.C.4. [*Received, September 21st*, 1950.]

70. *The Hydrogen–Calomel Cell. Part II. The Calomel Electrode.*

By G. J. Hills and D. J. G. Ives.

The calomel electrode has hitherto been too erratic in behaviour in dilute solutions to be used for measurements of precision with galvanic cells without liquid junction. It is shown that the calomel electrode is capable of a very high degree of reproducibility provided that various sources of error, which have been examined in detail, are eliminated. A theory of the mechanism of operation of the electrode is suggested.

The calomel electrode, introduced by Ostwald in 1890, was widely accepted as a reference electrode in the succeeding twenty years and had its heyday from 1910 to 1920. During this decade, however, the limitations of existing forms of the electrode were discovered and thereafter it fell gradually into disrepute as an instrument of precision.

Lewis and Sargent (*J. Amer. Chem. Soc.*, 1909, **31**, 362) found that the potential of the electrode depended upon the method of preparation and advocated rigid adherence to a given technique. Acree, Loomis, and Myers (*Amer. Chem. J.*, 1911, **46**, 585; 1913, **50**, 396) prepared a large number of calomel half-cells, using potassium chloride and hydrochloric acid solutions in cells with and without liquid junction, but found large deviations in potential from electrode to electrode; only by connecting the electrodes in parallel for long periods could they obtain an ostensibly reproducible potential. Their electrodes varied in sensitivity to mechanical disturbance. Ellis (*J. Amer. Chem. Soc.*, 1916, **38**, 737) used with advantage "electrolytic calomel," a dispersion of mercury and finely-divided calomel introduced by Hulett (*Phys. Reviews*, 1911, **32**, 257; *J. Amer. Chem. Soc.*, 1916, **38**, 20), who employed this type of preparation for mercurous sulphate in connexion with extensive studies of the Weston cell. Ellis chose insensitivity to movement as a criterion of reliability and obtained reproducibility within 0·05 mv., but his electrodes became highly erratic in hydrochloric acid weaker than 0·03N. Ming Chow (*ibid.*, 1920, **42**, 497) largely confirmed Ellis's work. Loomis and Meacham (*ibid.*, 1916, **37**, 2310) studied the hydrogen–calomel cell, standardising each measurement by reference to an aged standard calomel half-cell, but the actual reproducibility of the measurements was poor. Little improvement was shown by Loomis, Essex, and Meacham's work (*ibid.*, 1917, **39**, 1133). Similar rather unsatisfactory results were recorded by Lewis, Brighton, and Sebastian (*ibid.*, 1917, **39**, 2243) and Linhart (*ibid.*, 1919, **41**, 1175), and it was these workers who, with MacInnes and Parker (*ibid.*, 1915, **37**, 1445) and Harned (*ibid.*, 1922, **44**, 2729; 1926, **48**, 326), began to introduce the silver/silver chloride electrode as a more satisfactory alternative. Work on the calomel electrode continued, however, and Harned (*ibid.*, 1920, **41**, 1808), repeating some of Ellis's work, claimed considerable steadiness for his E.M.F.s, but the minimum deviation was no better than 0·20 mv.

All this work was carried out with solutions containing dissolved air; although the reaction $2Hg + 2HCl + \frac{1}{2}O_2 = Hg_2Cl_2 + H_2O$ was known, it was thought to be significant only at low concentrations (Ellis, Ming Chow, *locc. cit.*). This reaction had certainly precluded the determination of the standard E.M.F. of the hydrogen–calomel cell by means of an extrapolation to zero ionic strength and it did, in fact, vitiate nearly all the measurements with the calomel electrode carried out before 1922. This type of reaction is not restricted to hydrochloric acid, for even potassium chloride solutions, in presence of air, will dissolve mercury on long storage (Randall and Young, *ibid.*, 1928, **50**, 989; Gerke, *ibid.*, 1922, **44**, 1684).

In 1922 Gerke (*loc. cit.*) carried out the first reliable measurements with the calomel electrode, matching it against the silver/silver chloride electrode in cells containing thoroughly deoxygenated solutions of hydrochloric acid or potassium chloride. The E.M.F.s he obtained were independent of the electrolyte, but not of the method of calomel preparation, and, by using the known standard potential of the silver/silver chloride electrode, he gave the first reliable standard potential of the calomel electrode. In spite of this work, Harned in 1926 (*loc. cit.*) and Randall and Beckenbridge (*ibid.*, 1927, **49**, 1435) continued to record measurements using calomel electrodes in aerated solutions. The situation was clarified by the work of Randall and Young in 1928 (*loc. cit.*), who, using all three combinations of calomel, silver/silver chloride, and hydrogen electrodes in cells without liquid junction, fully established the damaging effects of dissolved air and showed that previous work on the hydrogen–calomel cell was largely worthless. They strongly advocated silver/silver chloride in replacement of calomel and were supported

by Mukherjee and Kumar (*ibid.*, 1930, **52**, 2179). No attempt has since been made to use the calomel electrode as an instrument of precision; almost all the important work on cells without liquid junction in the last two decades has employed the silver/silver chloride electrode, which is not, however, entirely free from some of the defects of its predecessor. Thus, it is sensitive to dissolved oxygen (Guntelberg, *Z. physikal. Chem.*, 1926, **123**, 199) and its potential is not independent of its mode of preparation (cf. Harned and Ehlers, *J. Amer. Chem. Soc.*, 1932, **54**, 1350). No serious attempt has been made to recover the calomel electrode from obsolescence, the only subsequent work of any value being that of Mueller and Reuther (*Z. Elektrochem.*, 1942, **48**, 220; 1943, **49**, 176), who confirmed Randall and Young's work (*loc. cit.*) and measured the E.M.F.s of the hydrogen–calomel cell with very careful technique involving the complete exclusion of oxygen. They claimed a reproducibility of 0·10 mv. and calculated the standard E.M.F. of the cell by making use of the activity coefficients of hydrochloric acid determined by Harned and Ehlers (*loc. cit.*).

As a reference electrode, the calomel half-cell is, of course, widely used in cells with liquid junction, and accuracy has been attained by calibration methods involving buffer solutions (MacInnes, Belcher, and Shedlovsky, *J. Amer. Chem. Soc.*, 1938, **60**, 1094; Hitchcock and Taylor, *ibid.*, 1937, **59**, 1812; 1938, **60**, 2710), although the potential of any one electrode remains somewhat uncertain.

From the considerations mentioned in Part I, and from its rather truncated history, it appeared that the potentialities of the calomel electrode had not been fully realised. The following work, of which a preliminary report has been made (Hills and Ives, *Nature*, 1950, **165**, 530), was undertaken to rectify this situation.

Studies of the Calomel Electrode.

There are five main sources of error affecting the calomel electrode, which, operating simultaneously, may produce deviations and randomness of potential of many millivolts.

(1) *Dissolved Oxygen.*—A cell was set up consisting of two calomel electrodes opposed to each other, containing thoroughly deoxygenated N/10-hydrochloric acid at 25°. The design of

Fig. 1.

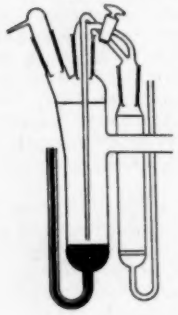
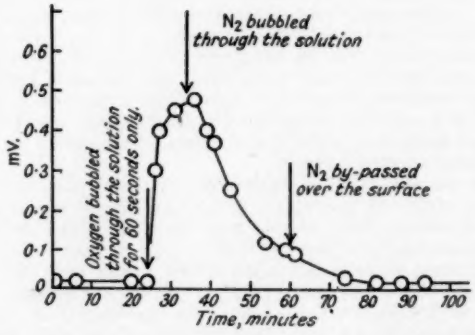


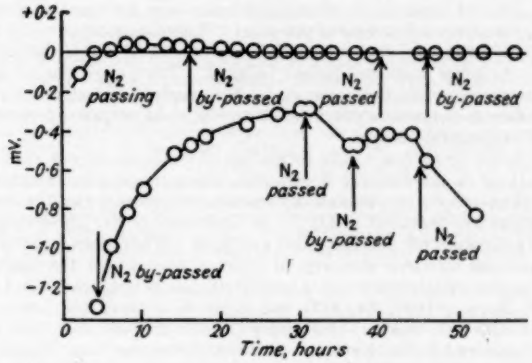
Fig. 2.



calomel half-cell used throughout this work is shown in Fig. 1; no platinum contact is immersed directly in the mercury pool of the electrode, and pure nitrogen from a presaturator may be bubbled through the solution or by-passed over its surface. The effect of passing oxygen for one minute through one half of the cell is shown in Fig. 2; the oxygenated electrode immediately develops a quite large positive potential with respect to the other. Although the reaction between mercury, hydrochloric acid, and oxygen is quite unable, in such a short period, significantly to deplete the bulk concentration of the acid, the effect of this reaction is immediately manifest at the mercury solution interface of the electrode. For short periods of oxygenation, therefore, the effect is reversible, the excess of positive potential falling to zero when the dissolved oxygen is swept out by nitrogen. It is desirable, nevertheless, that mercury should at no stage be brought into contact with oxygen-containing solutions.

(2) *Segregation.*—The classical method of preparing calomel electrodes has been in use for at least fifty years and consists of grinding or shaking mercury, calomel, and solution together to form a wet paste, which is deposited with the solution on a mercury pool. In the absence of specialised anaërobic technique (cf. Mueller and Reuther, *loc. cit.*), this involves a high degree of oxygenation and is further objectionable because the heavy layer of solid segregates a zone of solution close to the mercury surface. In an electrode system truly in equilibrium, this barrier to free exchange between the segregated region and the bulk of the solution might be harmless, but it magnifies the effects of any disequilibrium arising from the calomel and prevents normal response of the electrode to changes in the bulk solution (cf. Fales and Mudge, *J. Amer. Chem. Soc.*, 1920, **42**, 2434). The classical procedure gives an " untidy " electrode with a distorted mercury surface, changing in configuration with mechanical disturbance; the net effect is a highly erratic electrode very sensitive to movement. This point is illustrated in Fig. 3, in which the upper curve shows the E.M.F. of a symmetrical calomel–calomel cell with a very thin layer of calomel on each electrode; the lower curve relates to a similar cell in which the traditional paste was used for both electrodes. Thoroughly deoxygenated N/10-hydrochloric acid was used in each case, and other conditions were as alike as possible. It has in fact been found that an extremely thin layer of calomel is adequate and that it is unnecessary to

FIG. 3.



equilibrate the calomel with the cell solution or to saturate the cell solution with calomel before use.

(3) *Annular Solution Films.*—Many electrodes, prepared identically with avoidance of the two defects already described, still showed considerable differences of potential. These differences could nearly always be reduced by gently rocking the electrodes, but, in time, this treatment produced still larger deviations which could be removed by repeated rocking, and so on. It was obvious that the beneficial effect of this movement was to bring a wetted annulus between the mercury and the walls of the vessel into contact with the bulk of the solution.

Capillary action causes penetration of solution to considerable depths between mercury and the walls of the containing vessel. This occurs to such an extent that the area of the mercury/annular liquid-film interface may largely exceed the area of the interface which the mercury makes with the bulk solution, which alone is intended to be potential-determining. It is not to be expected that the conditions in such a constrained film will be the same as in the free solution. It is clear that, in an attempt to set up a two-phase equilibrium system, it is damaging if one of the phases is allowed partially to segregate into an enclave which cannot freely mix with the rest. When the system also involves a third, solid, phase, as in the calomel electrode, the possibilities of penetration and segregation are still further increased, especially if the solid phase is added in careless excess. This view is substantiated by the fact that the use of hydrophobic electrode vessels effected a very great improvement in the behaviour of the electrodes. This was achieved by treatment of the vessels with silicone fluid, by a method described in the experimental section, under conditions which ensured bonding between the silicone and the glass. With such vessels, no liquid annular film was formed; the solution

terminated sharply at a mercury/glass/solution line and there was a marked resistance to annulus formation on mechanical disturbance. The improvement resulting from this device is illustrated by comparing two groups of experiments, each involving a multitude of measurements, in terms of the mean deviation from the mean E.M.F.: these quantities were ± 13 μv. and ± 72 μv. for the hydrophobic and hydrophilic groups, respectively. The difference is an underestimate of the taming of the calomel electrode because many of the wilder vagaries were ignored. The use of " siliconed " glass may benefit many types of mercury electrode and may have virtue in reducing ion exchange between very dilute acid solutions and glass.

(4) *Calomel.*—Electrodes prepared with different samples of pure calomel continued to show discrepancies as large as 0·70 mv.; this common occurrence led Ellis (*loc. cit.*) to advocate the electrolytic preparation, which could be relied upon to give a product of reproducible properties, already equilibrated with mercury and hydrochloric acid. This material contains minute mercury droplets dispersed in calomel of crystal size 1—5 μ. Commercial " AnalaR " calomel, of uniform crystal size (*ca.* 50 μ.) appears to be unsuitable; it gives an electrode which is positive in potential to the " Ellis electrode," but the excess of positive potential decays asymptotically to zero over the course of days. Exhaustive equilibration with mercury and hydrochloric acid before use produced no improvement. Precipitated calomel of crystal size 1—5 μ., however, gave electrodes in excellent agreement with those prepared from the electrolytic calomel. It became clear that crystal size was the significant factor, but operating in the reverse direction to that expected from the normal solubility–size relationship.

It has been found that electrolytic calomel, on being kept for months, gives electrodes with gradually increasing positive deviations of potential. This is accompanied by the growth in the calomel of a yellow substance, which can be seen under the microscope in the form of yellow crystals much larger than the parent calomel. The yellow colour of old electrolytic calomel becomes apparent when it is ground, as, for example, between the cones of a ground joint. Again, the excess of positive potential of an electrode prepared from this aged material shows a very slow exponential decay.

This has been shown to be due to the formation of basic mercurous chloride, HgO,Hg_2Cl_2, which occurs naturally as the mineral Eglestonite, unequivocal identification being provided by *X*-ray powder photographs of new and old electrolytic calomel and the naturally occurring mineral. The authors are indebted to Dr. F. A. Bannister of the Mineralogy Department of the Natural History Museum for providing this evidence It had been expected that the yellow substance would contain mercuric mercury, in order to account for the positive deviations in potential which it produces, but the formula for Eglestonite is well established (Hillebrande and Schaller, *Amer. J. Science*, 1907, **24**, 272) and there is unassailable *X*-ray crystallographic evidence that it contains only mercurous mercury (Hedlik, *Experientia*, 1948, **4**, 66). The true explanation may therefore be that, by virtue of its oxide content, the " Eglestonite electrode " is reversible to oxide as well as chloride ions, and is therefore sensitive to pH. It may be regarded as the half-way house between the calomel and the mercury/mercurous oxide electrode. Since the latter has a standard potential of the order of 0·95 v. (M. de K. Thompson, *J. Amer. Chem. Soc.*, 1906, **28**, 731), the positive deviations are adequately explained; their decay with time is probably due to dissolution of mercurous oxide following the slow dissociation of Eglestonite into its components. Calomel precipitated chemically by the method described in the experimental section is less susceptible to these changes, which seem to occur when calomel is in contact with mercury, in air, under any but extremely dry conditions. Either electrolytic calomel or chemically precipitated calomel, in absence of this disturbing factor, gives electrodes which are identical in potential.

(5) *The Mercury–Calomel Interaction.*—It has been found essential to allow the mercury and calomel for an electrode to interact under dry conditions before the introduction of the solution. This has been carried out in practice by shaking together dry mercury and calomel for several minutes, whereupon a grey, adherent skin of calomel forms on the mercury. A very small amount of this skin introduced to clean, dry mercury spreads immediately over the whole available surface. Careful addition of solution, after displacement of air by nitrogen, then leads to a satisfactory electrode. This spreading skin is very characteristic in appearance and it seems to be an essential prerequisite for the formation of a completely depolarised calomel electrode. It is not formed if the period of interaction of mercury and calomel in the dry state is too brief, or if the crystal size of the calomel exceeds about 5 μ. (it is not formed by " AnalaR " calomel), or if moisture (let alone solution) is present. Comparative experiments were conducted with the same mercury, calomel, and solution brought together in different ways, and in all cases in absence of the preliminary dry interaction the electrodes were erratic,

positive in potential, and extremely sensitive to small mechanical disturbances, such as those caused by the bubbling of nitrogen. The effects were large, of the order of millivolts, but in all cases the electrodes gradually steadied with time and approached the proper potential. There is therefore strong evidence for the formation of some kind of bonding between the calomel and mercury which is essential for complete reversibility. This point is discussed in a later section.

It has been found that, provided the calomel electrode is prepared on the lines indicated, it is highly satisfactory, even in the most dilute hydrochloric acid solutions. It is simple to set up, reaches constant potential in 2—4 hours, is stable and reproducible to $\pm 10\,\mu$v., and shows no concentration polarisation effects such as those associated with the silver/silver chloride electrode (Smith and Taylor, *J. Amer. Chem. Soc.*, 1942, **64**, 3053).

Experimental.

Silicone Treatment of Electrode Vessels.—The thoroughly cleaned vessels were removed from the drying oven and, at a temperature of about 60°, were filled with a 1% solution of Dow–Corning Silicone Fluid No. 200 in redistilled carbon tetrachloride, emptied, drained, and heated at 165° ± 10° for two hours. After cooling, the vessels were repeatedly rinsed with freshly redistilled carbon tetrachloride, which was shown to remove completely any excess of unbonded silicone. The film so formed was intensely hydrophobic and seemed to be of indefinite life; it was, however, destroyed by successive treatments with nitric–chromic acid cleaning mixture and concentrated sodium hydroxide solution.

Electrolytic Calomel.—An electrolytic cell was set up in a 2-l. beaker, the cathode consisting of a cylinder of bright platinum foil enclosed in a guard tube. The anode consisted of a pool of pure mercury contained in a small beaker centrally placed in the cell, with a centrifugal stirrer arranged over it so as to skim the surface of the mercury and provide a powerful swirling of solution into and out of the small beaker. 2N-Hydrochloric acid was used as electrolyte, and was purified as described in the preceding paper. Electrolysis was carried out with an applied potential difference of 2 v.; on first application, without stirring, the mercury surface become multi-coloured and then formed a dark-grey, metallic-appearing skin. At this instant the current fell to zero (cf. Rothschild, *Proc. Roy. Soc.*, *B*, 1938, **125**, 283), but, on the mercury being stirred rapidly, was re-established at a steady value of *ca.* 0·5 amp., a dark-grey suspension of mercury and calomel being flung out of the anode compartment. After about two hours the electrolysis was stopped, the electrodes removed, and stirring continued for about 12 hours. The precipitate was allowed to settle, the electrolyte decanted off and replaced by fresh 2N-hydrochloric acid, and stirring continued for a further 6 hours. This was repeated and the calomel washed by decantation, first with the same acid and then with water. It was finally filtered at the pump, washed with water until the washings showed no test for chloride, drained, and dried in a vacuum. It was stored in the dark over phosphoric oxide. The hydrochloric acid used in this preparation must not be weaker than N. because of basic-salt formation (cf. Hulett and Gardiner, *Trans. Amer. Electrochem. Soc.*, 1928, **56**, 111, 129, 141).

Precipitated Calomel.—Excess of 2N-hydrochloric acid was added rapidly with vigorous mechanical stirring to a dilute solution of pure mercurous nitrate in dilute nitric acid standing over a pool of mercury. The precipitate was treated in the same way as the electrolytic calomel.

Mercury.—Commercial mercury, under dilute nitric acid, was subjected to aspiration of air for several days, dried, and distilled under reduced pressure of oxygen (delivered beneath the surface by means of a capillary), head and tail fractions being rejected. Batches were redistilled immediately before use in a small, all-glass vacuum still, swept out with nitrogen before evacuation.

Hydrochloric Acid Solutions.—These were prepared as described in the preceding paper.

Nitrogen.—The better grade of commercial nitrogen was fully deoxygenated by passing it over reduced copper in an electrically heated silica tube. Connections were made in the same way as for the hydrogen supply (described in Part I).

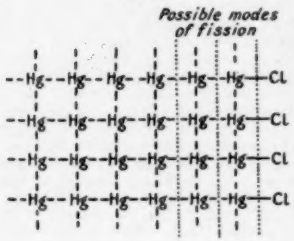
The potentiometric apparatus and general procedure are fully described in Part III (succeeding paper).

Discussion.

The calomel electrode is traditionally regarded as a mercury/mercurous-ion electrode at which the activity of mercurous ions is reciprocally linked to that of chloride ions by the presence of solid mercurous chloride, with which the solution is saturated. The standard potential of the calomel electrode is related to that of the mercury/mercurous-ion electrode by $E^{\circ}_{\text{calomel}} = E^{\circ}_{\text{Hg, Hg}_2^{++}} + \frac{RT}{2F} \log_e K_s$, where K_s is the thermodynamic solubility product of calomel. This relationship is thermodynamically rigid, but it does not necessarily define the mechanism by which the calomel electrode works: all that can be said is that the true mechanism, whatever it may be, must fit into this thermodynamic framework. The idea that the calomel electrode works by the charge and discharge of mercurous ions leads to difficulties. The values of the standard electrode potentials of 0·2680 v. and 0·7896 v. being taken for the calomel and mercury/mercurous-ion electrodes respectively, it follows that the activity of mercurous ions in equilibrium with the standard calomel electrode is of the order 10^{-18} g.-ion/l., or about

600 mercurous ions/c.c. If it be assumed that a mercurous ion needs to be within 10 A. of a mercury surface before it can discharge upon it, it further follows that the duty of depolarising about 35 *square metres* of mercury surface devolves upon each mercurous ion. Even with due regard to the provision of mercurous ions by a mobile equilibrium, it seems evident that the calomel electrode can hardly operate to any significant extent by means of the classical mechanism, and it becomes necessary to consider what ions are present in sufficient quantity to depolarise the electrode. Since it is probable that calomel is not highly dissociated and the second dissociation will be much less than the first, and since chloride ions are present in overriding excess, the chloromercurous ion, Hg_2Cl^+, will be present in significant amount. Jonsson, Qvarfort, and Sillén (*Acta Chem. Scand.*, 1947, **1**, 461) could not experimentally confirm the existence of the chloromercurous ion and concluded that the equilibrium constant for the reaction $Hg_2Cl_2(\text{solid}) + Hg_2^{2+} \rightleftharpoons 2Hg_2Cl^+$ must be less than $0{\cdot}5 \times 10^{-6}$ g.-ion/l. But even if this constant is as low as 10^{-12}, a solution containing 0·001 g.-ion/l. of chloride, in equilibrium with solid calomel, will contain a concentration of chloromercurous ions at least equalling that of mercurous ions and becoming very much greater for higher values of the above equilibrium constant or of the chloride-ion concentration. It can readily be shown that although the system at equilibrium must contain mercuric ions, their concentration is infinitesimal and cannot be mechanistically significant, but, as shown by Jonsson, Qvarfort, and Sillén (*loc. cit.*), they are greatly exceeded in concentration by chloromercuric ions, $HgCl^+$. It may be concluded that the main ionic entities in equilibrium with the calomel electrode are chloride, chloromercurous, and chloromercuric ions.

FIG. 4.



It is now suggested that one or more of these ions comes into equilibrium with mercury by means of an intermediary which may be called "chloromercury," consisting of a monolayer of chlorine atoms covalently bound to the mercury surface: Fig. 4 indicates formally how alternative modes of fission might allow such a system to come into equilibrium with the appropriate solution ions. It is further suggested that it is this chloromercury structure, which is not spontaneously formed except under special conditions, which is the essential prerequisite for the formation of a fully depolarised, reversible calomel electrode. Some points of evidence may be presented.

The behaviour of mercury on anodic polarisation in hydrochloric acid is very characteristic and stands in strong contrast to that of silver. With mercury, after the passage of a few hundred millicoulombs/sq. cm., a sudden, blocking polarisation takes place and the current falls to zero (cf. Rothschild, *loc. cit.*, and, in the experimental section, the preparation of electrolytic calomel) and is only restored by mechanical disruption of the surface. On the other hand, metallic silver may, under the same conditions, be smoothly converted into silver chloride. Since silver is univalent, every discharged chloride ion removes a silver atom from its place in the metal lattice, leaving a fresh site at which further discharge can occur. For mercury, however, every discharged chloride ion does not saturate the valency of the metal atom to which it attaches itself; the metal atom is not removed, no fresh site is generated, and complete polarisation occurs when the mercury surface is covered by a monolayer of chlorine atoms. No doubt this picture is idealised; local disruptions of the film may occur and competing charging processes for mercurous and chloromercurous (or chloromercuric) ions may take place, leading to the formation of the macroscopic, if small, quantities of calomel which are in fact observed. Nevertheless, the anodic current suddenly falls to a vanishingly small magnitude, and this could not occur if the disruptions or charging processes took place readily.

If this chloromercury film is to be advanced as the essential intermediary in the operation of the calomel electrode, it must be shown capable of satisfying the demands which this electrode in fact meets; this is clearly a very critical question in relation to a proposed "monolayer electrode." The number of atoms per sq. cm. of a mercury surface is of the order of 10^{15} and a half-populated monolayer of chlorine atoms residing thereon would contain about 8×10^{-10} g.-atoms of chlorine, which, on charge or discharge, would involve the transfer of about 8×10^{-5} coulomb, which is ample to satisfy the demands of normal potentiometry. The calomel electrode will in fact satisfy without permanent damage much heavier demands (but not in the course of accurate potentiometric measurements), and this must involve monolayer repair with the aid of crystalline calomel which is always present. It is suggested that a partially populated monolayer is in thermodynamic equilibrium with solid calomel, but that, under the conditions

prevailing in the calomel electrode, this equilibrium is not rapidly established and, unless it is established either by long storage or by suitable preliminary treatment, the electrodes shows unsatisfactory behaviour.

A further aspect of the proposed electrode mechanism that requires comment is that, since it involves the making and breaking of covalent bonds, some transition process of low activation energy must be found. Such a process is illustrated in Fig. 5, showing a chloride ion in the close vicinity of a mercury surface. Two potential-energy curves are shown, that on the right relating to a hydrated chloride ion and that on the left to a discharged chloride ion which has become a chlorine atom covalently bound to the mercury surface. The minima of these curves are defined on the energy scale by, respectively, the electron affinity of chlorine plus the hydration energy of the chloride ion and the thermionic work function of mercury plus the energy of the surface covalent binding. The magnitudes of these quantities, as far as they are known, do not exclude the possibility that, when the equilibrium potential difference has been established between the mercury and the solution, these two minima are at approximately equal energy levels and are separated by only a small energy barrier at the point of intersection of the two curves. The argument is similar to that relating to the hydrogen electrode (cf. Part I, preceding paper), but has the important difference that the metal surface is homogeneous and the energy of binding of the discharged atom to the surface should be fixed, unless repulsion between attached atoms leads to a non-constant differential binding energy.

FIG. 5.

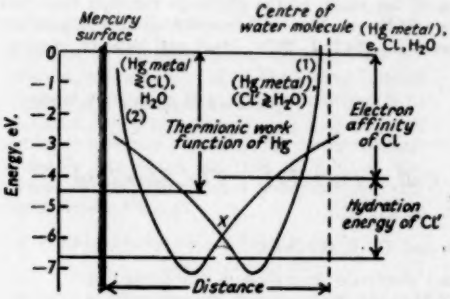
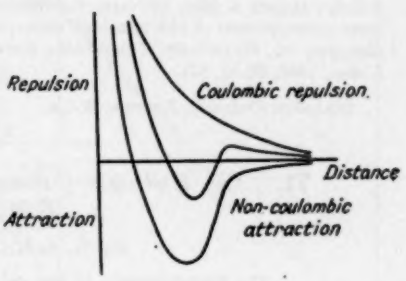


FIG. 6.



An alternative, and perhaps more probable, mechanism may involve chloromercurous (or even chloromercuric) ions rather than chloride, but no direct means can be seen of distinguishing between these possibilities, each of which, however, involves chloromercury.

Discussion of the theory may be concluded with the following ancillary evidence.

(1) It has been shown that special techniques of preparation are necessary to obtain a completely depolarised calomel electrode, and this points circumstantially to the need for some special relationship between mercury and calomel which is not established spontaneously in all circumstances. In particular, there is no doubt at all about the very profound effect of preliminary dry interaction, which, it is believed, results in the formation of chloromercury. It has been pointed out by Gurney (*J. Physical Chem.*, 1938, **6**, 499) that the force–distance curve for the atoms in the mercurous ion must be compounded from coulombic repulsion between like-charged atoms and the non-coulombic exchange forces of covalent binding and will be of the form shown in Fig. 6. The mercurous ion may therefore undergo ready fission (cf. Pauling's adjacent charge rule), although the electrostatic repulsion will be greatly weakened by hydration. Similar considerations may apply to the calomel molecule. If such a molecule be imagined situated close to, and parallel with, a mercury surface, interactions may occur as a result of the tendency of the calomel mercury atoms to form metallic bonds. If the intramolecular bond between the mercury atoms is sufficiently weak, fission may occur, allowing the mercury atoms to enter the bulk phase and leading to two chlorine atoms covalently bound to the mercury surface. It is for this process that water may be inhibitory, virtually eliminating the electrostatic (dipole–dipole) repulsion on which the fission depends. It must be admitted, on the other hand, that preferential adsorption of water at the mercury surface may play a contributory or decisive rôle. It has been found that fine subdivision of the

calomel is necessary for this interaction: if some special orientation of calomel molecules with respect to the surface is necessary and if only one crystal plane will supply molecules in suitable array, then very fine subdivision will ensure, statistically, satisfaction of the special geometrical requirement.

(2) It has been found experimentally that the anomalous positive increment in potential of faulty calomel electrodes can be removed by small anodic or cathodic polarisations. This is striking evidence in favour of the chloromercury structure, which is the only conceivable single product of the discharge of oppositely charged ions (chloride or chloromercurous, respectively).

(3) The classical method of preparation of the calomel electrode, involving grinding the components together in air, has been condemned, but the fact remains that it is satisfactory, within limits, for many purposes. It seems probable that the aeration in the grinding technique may have one beneficial effect: that the mercury–hydrochloric acid–oxygen reaction proceeds at the mercury surface to give the chloromercury film. Certainly the immediate result of excluding oxygen from the electrode, without attending to any of the other requirements, is a marked deterioration, the wildest variations in electrode potential being observed.

(4) There is much evidence in the literature for the specific adsorption of halide ions on mercury, which may have its root in the tendency to form covalent bonds (Grahame, *Chem. Reviews*, 1947, **41**, 283). The dropping-mercury electrode has often been studied in halide-containing solutions (Kolthoff and Lingane, "Polarography," Interscience, 1946, p. 322) and, when acting as anode, it shows marked dependence, both in current–voltage relationship and in mechanical behaviour, on the halide present (Bockris and Parsons, *Nature*, 1947, **160**, 232), which suggests a more intimate participation of the anion in the electrode reaction than the mere precipitation of the insoluble mercurous salt by reaction with mercurous ions formed by charging (cf. Heyrovsky, *Discussions Faraday Soc.*, 1947, **1**, 212; Haul and Scholtz, *Angew. Chem.*, 1948, **60**, *A*, 65).

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71. *The Hydrogen–Calomel Cell. Part III. The Standard E.M.F. at 25° c.*

By G. J. Hills and D. J. G. Ives.

The improvements in the calomel electrode described in the preceding paper have allowed the standard E.M.F. of the hydrogen–calomel cell at 25° to be determined by direct extrapolation of the experimental measurements to zero ionic strength. The standard free energy of formation of mercurous chloride and the activity coefficients of aqueous hydrochloric acid at 25° have been re-evaluated.

Methods by which many of the difficulties associated with the calomel electrode have been circumvented are described in the preceding paper. The resulting improvement in reproducibility of the electrode warranted an attempt to extend measurements of the E.M.F. of the cell H_2,Pt|HCl(aq.)|Hg_2Cl_2|Hg into regions of high dilution, with the object of determining the standard E.M.F. by direct extrapolation to zero ionic strength.

Measurements have been made over the concentration range 0·1—0·002N., the lower limit being set by the effects of ion exchange between the acid solutions and the glass of the containing vessels. In contrast to previous experience, no loss of reproducibility was encountered with decreasing concentration, and an accurate extrapolation gave, for the standard E.M.F., the values $E^0_m = 0{\cdot}26796$ and $E^0_c = 0{\cdot}26781$ absolute volt at 25° c., on the molality and molar concentration scales respectively, with an estimated error not exceeding $\pm 0{\cdot}00001$ v.

The measurements from which these results were derived are given in Table I.

Table I.

Molality of HCl.	E.M.F., abs. v.	Molality of HCl.	E.M.F., abs. v.	Molality of HCl.	E.M.F., abs. v.
0·119304	0·38948	0·037690	0·44516	0·0076938	0·522675
0·094276	0·40088	0·025067	0·46490	0·0050403	0·543665
0·075081	0·41187	0·018871	0·47870	0·0030769	0·56825
0·064718	0·41906	0·013968	0·49339	0·0016077	0·60080
0·051645	0·42994	0·0109474	0·50532		

Some difficulty arises in selecting values for the fundamental constants to be used in these calculations. Birge's values (*Rev. Modern Physics*, 1941, **13**, 233) have been adhered to and, with other relevant quantities, are collected in Table II.

TABLE II.

Absolute temperature corresponding to 0° C.	273·16° K.
J, abs. joules/15°-cal.	4·1855
Electronic charge, **e**, e.s.u.	$4{\cdot}8025 \times 10^{-10}$
Avogadro's number, *N*	$6{\cdot}0227 \times 10^{23}$
Faraday, *F*, abs. coulombs/equiv.	96,487
Boltzmann constant, *k*, erg/degree	$1{\cdot}38047 \times 10^{-16}$
Molar gas constant, *R*, abs. joules/mole/degree	8·31436
Absolute volt/international volt	1·00034
Absolute joule/international joule	1·00019
Dielectric constant, *D*, of water at 25° C.	78·54
Density of water, ρ_0, g./ml. at 25° C.	0·997071
Debye–Hückel constant *A* for water at 25° C.	0·5091
Debye–Hückel constant β for water at 25° C.	0·3286

The method of extrapolation to zero ionic strength suggested by Hitchcock (*J. Amer. Chem. Soc.*, 1928, **50**, 2076) and used by Harned and Ehlers (*ibid.*, 1932, **54**, 1350; 1933, **55**, 652, 2179) in the determination of the standard E.M.F. of the cell H_2,Pt|HCl(aq.)|AgCl|Ag is based upon the modified Debye–Hückel expression:

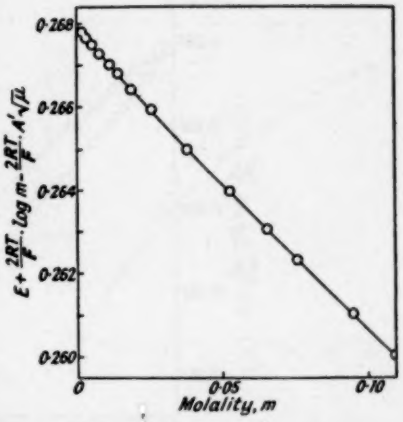
$$\log_{10}\gamma_{\pm} = -A'\sqrt{m} + Bm \quad . \quad . \quad . \quad . \quad (1)$$

where $\gamma_{\pm}$ is the mean molal ionic activity coefficient, m is molality, A' is the Debye–Hückel constant proper to ionic strength calculated in terms of molality ($A' = A\sqrt{\rho_0}$) and B is an arbitrary constant. Substitution in the thermodynamic expression for the E.M.F. of the concentration cell without transport and rearrangement leads to

$$(E + 0{\cdot}118319 \log_{10}m - 0{\cdot}118319\, A'\sqrt{m}) = E^0_m - 0{\cdot}118319\, Bm \quad . \quad . \quad (2)$$

where E is the measured E.M.F. at molality m and E^0_m is the standard E.M.F. on the molality scale. The quantity on the left-hand side of equation (2) is a linear function of m insofar as equation (1) is valid. Treated in this way, the present results for the hydrogen–calomel cell give the curve shown in Fig. 1. The plot is not linear and shows no sign of conforming more closely to equation (2) with decreasing concentration. An extrapolation on this basis is therefore unsatisfactory and cannot fix the value of E^0_m more closely than $\pm 0{\cdot}05$ mv., which is in fact the uncertainty attributed by Harned and Ehlers to their own extrapolation by this method. There seems little reason to suppose that equation (1) holds accurately over any concentration range and it is unjustifiable to apply the method of least squares to such an extrapolation (cf. Scatchard and Prentiss, *Chem. Reviews*, 1933, **13**, 139).

FIG. 1.



An alternative method first suggested by MacInnes and Brown (*J. Amer. Chem. Soc.*, 1935, **57**, 1356) is better founded in that it uses the full, but unextended, Debye–Hückel expression:

$$\log_{10}\gamma_{\pm} = -\frac{A'\sqrt{m}}{1 + \beta' a_i\sqrt{m}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

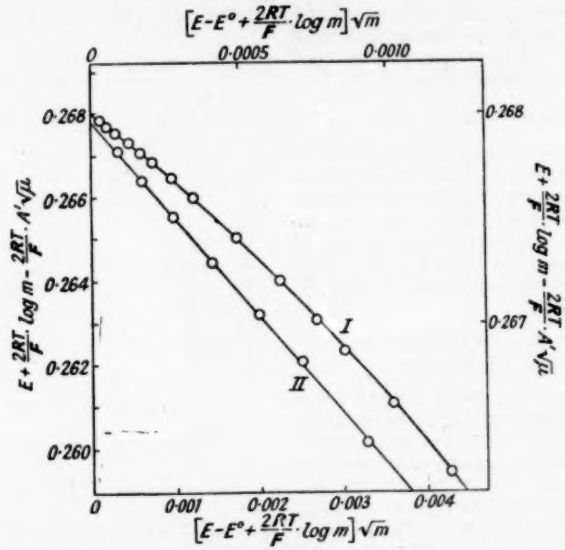
where β' is again the appropriate Debye–Hückel constant adjusted to ionic strength expressed on the molality scale ($\beta' = \beta\sqrt{\rho_0}$) and a_i is the distance of closest ionic approach. Substitution in the thermodynamic expression for the E.M.F. of the concentration cell without transport and rearrangement leads to

$$[E + 0{\cdot}118319 \log_{10}m - 0{\cdot}118319\, A'\sqrt{m}] = E^0_m - \beta' a_i\sqrt{m}[E - E^0_m + 0{\cdot}118319 \log_{10}m] \quad . \quad (4)$$

A plot of the left-hand side of this equation against the quantity $\sqrt{m}[E - E^0_m + 0{\cdot}118319\log_{10}m]$ should give a straight line of slope $\beta' a_i$ and intercept E^0_m. In using this method, it is necessary to conduct a short series of successive approximations until the value of E^0_m used in computing the abscissæ agrees with the value derived from the intercept. The method has been applied to the present measurements on the hydrogen–calomel cell, with the results shown in Fig. 2, Curve I. It is seen that the plot deviates from linearity at abscissæ exceeding 0·001, but below this (corresponding with molalities lower than 0·02) becomes strictly linear. This section is plotted separatedly on a larger scale (Curve II, upper and right-hand axes). The final extrapolation was checked by the " zero sum " method and gave $E^0_m = 0{\cdot}26796$ abs.v. The entire calculation and extrapolation was carried out independently in terms of molar concentrations instead of molalities and gave $E^0_c = 0{\cdot}26781$ abs.v., in complete agreement with the relation $E^0_c = E^0_m \rho_0$.

A similar extrapolation has been carried out using Harned and Ehlers's data (*loc. cit.*) on the hydrogen–silver chloride cell and is shown in Fig. 3. MacInnes (" The Principles of Electrochemistry," Reinhold Publishing Corp., 1947, p. 186), remarking on the rather wide deviations,

FIG. 2.



blames the hydrogen electrode " the variations of which are probably the chief cause of the scattering of the points." It is doubtful if this was the case; in the present work no such loss in reproducibility at lower concentrations was observed and it seems more likely that the silver/silver chloride electrode was the source of error. If this is the case, the silver/silver chloride electrode appears to be considerably inferior to the calomel electrode.

The slope of the MacInnes and Brown plot may be used to obtain the distance of closest ionic approach, a_i. The present results lead to $4{\cdot}96 \pm 0{\cdot}01$ A. for aqueous hydrochloric acid, which is not in good agreement with the value of 5·62 A. obtained by MacInnes and Shedlovsky (*J. Amer. Chem. Soc.*, 1936, **58**, 1970) from work on cells with liquid junction, or with the value of 5·50 A. calculated from Harned and Ehlers's results (*loc. cit.*). It may be pointed out, however, that greater uncertainty must attach, on the one hand to data affected by liquid-junction potentials and, on the other, to the slopes of best straight lines drawn through points showing divergences as great as those in Fig. 3.

The new value for the standard E.M.F. of the hydrogen–calomel cell does not represent any important change. Bockris and Herringshaw (*Discussions Faraday Soc.*, 1947, **1**, 328), in a critical summary of recorded electrode potentials, give $E^0 = 0{\cdot}268$ v. for the calomel electrode. There is correspondingly little change in the calculated standard free energy of formation of

mercurous chloride. The standard free energy of the cell reaction from the new value of E°_m is $-12{,}391$ cals. By using $-31{,}350$ cals. for the standard free energy of formation of the chloride ion in aqueous solution ("Values of Chemical Thermodynamic Data," U.S. National Bureau of Standards, Series I, 1947), there is obtained:

$$2Hg + Cl_2 = Hg_2Cl_2;\ \Delta G^\circ = -50{,}309 \text{ cals.}$$

This results is slightly lower than the value, $-50{,}350$ cals., given by the Bureau of Standards (*loc. cit.*), and is advanced as of improved accuracy.

Activity coefficients of hydrochloric acid in aqueous solution at 25° have been calculated from the measured and standard E.M.F.s of the hydrogen–calomel cell and are shown in Table III.

TABLE III.

Molality of HCl.	Mean molal act. coeff.	Molality of HCl.	Mean molal act. coeff.	Molality of HCl.	Mean molal act. coeff.
0·119304	0·7876	0·037690	0·8436	0·0076938	0·9140
0·094276	0·7984	0·025067	0·8639	0·0050403	0·9276
0·075081	0·8095	0·018871	0·8772	0·0030769	0·9416
0·064718	0·8163	0·013968	0·8903	0·0016077	0·9568
0·051645	0·8278	0·0109474	0·9002		

FIG. 3.

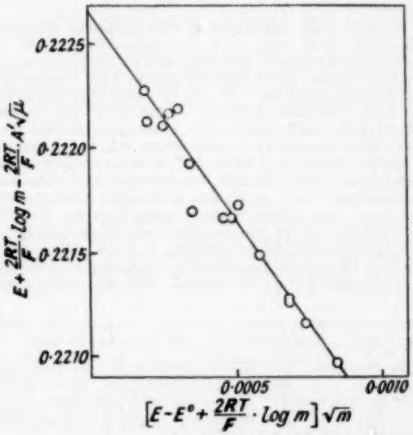
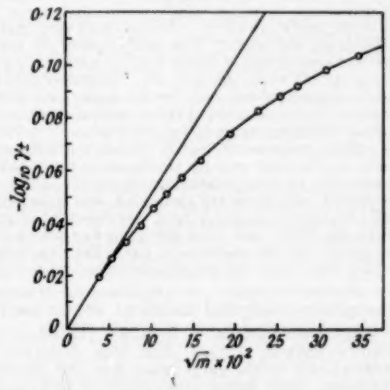


FIG. 4.



Values of $\log_{10}\gamma_\pm$ are plotted against the square root of molality in Fig. 4. The limiting slope of the plot is $0{\cdot}5079 \pm 0{\cdot}0010$, which agrees satisfactorily with the theoretical value of 0·5084. Although this cannot be taken as an independent evaluation of the Debye–Hückel constant, it shows the complete consistency of the data with the limiting theory. No attempt has been made to apply any of the extended equations. Activity coefficients at rounded molalities have been interpolated from a large-scale plot of the type of Fig. 4 and are compared with the figures given recently by Harned and Owen ("The Physical Chemistry of Electrolytic Solutions," Reinhold Publishing Corp., 2nd. Edn., 1950, pp. 340, 547) in Table IV.

TABLE IV.

Mean molal activity coefficients of aqueous hydrochloric acid at 25° C.

m.	$\gamma_\pm$, present work.	$\gamma_\pm$, Harned & Owen.	m.	$\gamma_\pm$, present work.	$\gamma_\pm$, Harned & Owen.
0·0001	0·9884	0·9891	0·04	0·8406	—
0·0002	0·9836	0·9842	0·05	0·8296	0·8304
0·0005	0·9745	0·9752	0·06	0·9205	—
0·001	0·9650	0·9656	0·07	0·8129	—
0·002	0·9519	0·9521	0·08	0·8064	—
0·005	0·9280	0·9285	0·09	0·8007	—
0·01	0·9040	0·9048	0·10	0·7958	0·7964
0·02	0·8747	0·8755	0·11	0·7914	—
0·03	0·8551	—	0·12	0·7874	—

Although the discrepancies between the two sets of figures are not large, their effect is shown by the calculation of E°_{m} from each experimental E.M.F. of the hydrogen–calomel cell, the Harned and Owen activity coefficients being used. The results show a systematic trend, ranging from 0·26805 v. at $m = 0{\cdot}12$ to 0·26795 v. at $m = 0{\cdot}002$. This probably arises because the Harned and Owen activity coefficients do not seem to have been recalculated with the new value of $2RT/F$ required by the revision of the fundamental constants by Birge in 1941 (*loc. cit.*).

Experimental.

Fundamental Standards and Instruments.—(*a*) *Mass.* All weights were corrected by reference to standards certified within 1 part in 10^6 by the National Physical Laboratory. Weighings of primary analytical standards were made to 0·01 mg. by a substitution method and were corrected to vacuum. All solutions were prepared by weight, and densities were determined for the calculation of molar concentrations.

(*b*) *Pressure.* Barometric pressures were measured by means of a barometer, at the same level as the apparatus, calibrated by a series of readings from Kew Observatory. Errors in pressure measurements were equivalent to less than 5 μv. variation in hydrogen-electrode potential.

(*c*) *Temperature.* A bomb calorimeter thermometer was provided with a special calibration to within $\pm$0·002° c. at 25° c. by the National Physical Laboratory. This was independently checked against a platinum resistance thermometer calibrated in the laboratory against ice, steam, and sodium sulphate with agreement to within $\pm$0·005° c. A water-filled thermostat was used and maintained at 25° $\pm$ 0·005° c.

(*d*) *E.M.F.* The two components of a double Weston cell, calibrated at the National Physical Laboratory, were in very precise agreement with each other and with the standard E.M.F. of 1·01831 abs.v. at 25° c. The cell was mounted in a Dewar vessel and left undisturbed throughout the course of the work. The temperature of the cell was taken when measurements were made, the potentiometer being fitted with a temperature-compensating rheostat. A new Tinsley potentiometer (type 4025) was used and was calibrated internally by a standard method. A check on the overall standardisation was kept by arranging one of the standard cells for use in the measuring circuit; the potentiometer was found to be extremely stable, apart from a small zero error which was measured on every occasion that readings were taken. A Tinsley galvanometer (type S.S. 545) was used, not only as a null-point detector, but to obtain the last significant figure in the E.M.F. measurements. This was done in a manner exactly analogous to the " method of swings " in weighing and is thought to be greatly preferable to final potentiometric subdivision by slide-wire : the $\pm$0·05 microcoulomb involved in each observed galvanometer deflection was a negligible infringement of the requirement of reversibility. All potentiometric equipment was mounted on an " equipotential surface " (White, *J. Amer. Chem. Soc.*, 1914, **36**, 2011), and close attention was paid to insulation, liberal use being made of polythene. Before immersion in the thermostat bath, the experimental cells were externally treated with silicone grease, which effectively eliminated insulation difficulties.

Materials.—*Silver.* A special sample of assay silver of 99·997% purity (Johnson Matthey) was used as a primary analytical standard. It was fused to a mirror-bright button in hydrogen before use.

Potassium chloride. " AnalaR " potassium chloride was freed from other halogens by Pinching and Bates's method (*J. Res. Nat. Bur. Standards*, 1946, **37**, 311) and recrystallised three times from conductivity water, large head and tail fractions being discarded. The dried salt was fused in a platinum vessel in an atmosphere of hydrogen, and was used as a secondary analytical standard. Comparison with the silver by analysis gave an atomic ratio Cl/Ag = 0·99992.

Water. Conductivity water was prepared in a Pyrex still of the Stuart and Wormwell type (*J.*, 1930, 85) and was used in the preparation of all solutions.

Hydrochloric acid, mercury, calomel, hydrogen, and nitrogen. These were prepared for use in the manner described in the previous Parts.

General Arrangements and Ancillary Apparatus.—The hydrogen-electrode assembly and buffer vessel containing the guard hydrogen electrode (Part I) were combined with two calomel electrodes (Part II) to form the complete all-Pyrex cell, the two halves of which were separated by a wide-bore vacuum tap, well lubricated with silicone or " Apiezon L " grease. This tap was opened only momentarily for E.M.F. measurements to be made. It provided perfect insulation, and no evidence was found of ill-effect either from exchange of solution between the two half-cells or from contamination of the electrodes by tap grease. Independent filling tubes were provided for the half-cells, flow of solution through the tap never being allowed. Each of the four electrode vessels was provided with a presaturator and the means of bubbling the appropriate gas through the solution or by-passing it over the surface. The cell was fitted with a *B*29 standard ground cone sealed to the base of the buffer electrode vessel, so that the whole cell, centrally suspended, could be " plugged " into a socket rigidly mounted in the bottom of the thermostat tank. This device greatly facilitated handling of the cell and was effective in minimising vibration. Solutions were prepared and stored in 5-l. or 2-l. Pyrex flasks, fitted with heads so arranged that nitrogen from a scrubber and presaturator could be bubbled through the solution, by-passed over its surface, or used to develop a pressure to blow the solution in a controlled manner through a delivery tube for cell filling. Delivery tubes of polyvinyl chloride were used; they are hydrophobic and unobjectionable for this purpose.

Connections between the electrodes and the potentiometer were made by means of screened, polythene-insulated cable and a selector switch so arranged that readings could be taken in rapid

succession of E.M.F.s between (*a*) the four possible combinations of hydrogen and calomel electrodes, (*b*) the hydrogen electrodes proper and the guard electrode in the buffer vessel, and (*c*) any pair of like electrodes, hydrogen or calomel. The criterion was adopted of rejecting all measurements for which the concordance between like electrodes was not within 20 μv.

Procedure.—The hydrochloric acid solutions were kept in the storage flasks with presaturated nitrogen passing for at least 48 hours before use. Analysis was carried out during this period. The preparation of the cell for use has been described in the preceding papers. After introduction of the freshly distilled mercury into the calomel-electrode vessels, a further quantity was pipetted into a clean, glass-stoppered Pyrex bottle and shaken vigorously for two to four minutes with a small quantity of calomel taken directly from the desiccator. Some of the resulting grey " skin " was introduced to each mercury surface by means of a small glass ladle. Instantaneous spreading occurred. The four presaturators filled with the cell solution were attached and the cell transferred to the thermostat with the minimum of shaking. The all-glass connections to the hydrogen and nitrogen supply lines were made and the cell swept out thoroughly with these gases. The electrode vessels were then filled, catalyst added to the appropriate vessel, and the two normal hydrogen electrodes fitted. Hydrogen and nitrogen were bubbled through the solution in the proper half-cells. E.M.F. readings were taken at intervals of 10 minutes, the gases being by-passed over the solution, and became constant in about 2 hours. Readings were continued at intervals for a few hours and the cell left overnight with the gases by-passing the solutions. Slight changes of E.M.F. sometimes occurred overnight, due to imperfection in the gas presaturation arrangements, but these were rectified by cell refilling, and a further set of measurements was carried out. Agreement of results obtained on different days was almost invariably excellent. The only systematic exception arose from the effects of ion exchange between very dilute solutions and the glass of containing vessels. At concentrations exceeding 0·005N., this is inappreciable; between 0·005N. and 0·001N., it is slight and was countered by an extrapolation to zero time. Corrections of this type were applied to the results from the two most dilute solutions and amounted to 20 and 35 μv.

Analysis of Solutions.—Expression of the E.M.F. data to five significant figures required a knowledge of the concentration of hydrochloric acid to an accuracy of 3 parts in 10,000. Use was made of MacInnes and Dole's differential titration method (*J. Amer. Chem. Soc.*, 1929, **51**, 1119), which allows the equivalence point in silver/chloride titrations to be detected unambiguously to 1 part in 10,000.

About 3 g. of silver were dissolved in dilute nitric acid in a tared, closed flask. Nitrous acid was removed from the resulting solution by addition of 0·2 g. of urea and sodium hydroxide solution was added to neutralise the excess of nitric acid. The slightly acid solution (*ca.* 0·01N. with respect to nitric acid) was diluted to 250 ml., and the flask and contents weighed. An accurate blank was carried out on all reagents for traces of chloride and an appropriate small correction applied.

The standard silver nitrate solution was delivered from a weight burette into the titration beaker, diluted to 250 ml., and stirred by a motor-driven glass paddle. The hydrochloric acid solution to be analysed was added dropwise from a second weight burette until a very small excess of silver nitrate remained. The suspension of silver chloride was stirred in the dark for one hour. Two silver/silver chloride electrodes were then introduced, one in the main bulk of the solution and the other enclosed in a " pipette," which could be filled with, and emptied of, solution by means of an attached rubber bulb. The residual E.M.F. between these two electrodes in the same solution was frequently measured throughout the analysis and, although it seldom exceeded a few tenths of 1 mv., was applied as a correction to all the significant differential E.M.F.s. The precise end-point was determined by using tenfold weight dilutions of the reagents, added in small constant volumes (0·10—0·20 ml.) from micro-burettes, the difference in potential between the electrodes after each addition of titrant being recorded and the pipette being flushed after each such reading to bring the difference in potential to zero. Regular curves were obtained, enabling the equivalence point to be interpolated to an accuracy on the whole analysis of 1 part in 25,000. For each analysis the mean of four end-points was taken, obtained in two titrations with each of the reactants as titrant. The agreement between such end-points was well within the required limits of accuracy. A trial estimation, in which the main precipitation was carried out (*a*) by adding silver nitrate solution to the hydrochloric acid, (*b*) by the reverse addition, and (*c*) by adding both reactants slowly and simultaneously to water, showed that adsorption errors were negligible.

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72. *Constitution of the Mucilage from the Bark of* Ulmus Fulva (*Slippery Elm Mucilage*). *Part III. The Isolation of* 3-*Monomethyl* D-*Galactose from the Products of Hydrolysis.*

By E. L. HIRST, L. HOUGH, and J. K. N. JONES.

The isolation and characterisation of 3-methyl D-galactose, a component of Slippery Elm mucilage, is described.

AN investigation of the hydrolysis products of slippery elm mucilage by Anderson (*J. Biol. Chem.*, 1933, **104**, 163) revealed that D-galacturonic acid, D-galactose, L-rhamnose, and a partially methylated aldose were constituent monosaccharide units. Constitutional studies were

continued by Gill, Hirst, and Jones (Part I, *J.*, 1939, 1469) who, as the result of a graded hydrolysis of the mucilage, succeeded in isolating an aldobiuronic acid, identified as 2-D-galacturonosido-L-rhamnose. Conversion of the mucilage into the fully methylated derivative by the thallium procedure, followed by hydrolysis, gave a complex mixture of methylated monosaccharides containing only galactose, rhamnose, and galacturonic acid derivatives (Part II, *idem, ibid.*, 1946, 1025). The identity of the sugar containing the methoxy-groups was therefore unknown, and the present paper is concerned with the characterisation of this sugar.

The acidic polysaccharide obtained by repeated precipitation from acidified alcohol contained 3·3% of methoxyl groups. Acidic hydrolysis of this polysaccharide afforded a mixture of reducing sugars (*A*; see Experimental section), in addition to D-galacturonic acid and 2-D-galacturonosido-L-rhamnose. After separation from the acidic materials, the mixture of sugars was separated by paper partition chromatography, and from the rate of movement of the sugars and from the colours produced on reaction with a variety of specific spray reagents (Hough, Jones, and Wadman, *J.*, 1950, 1702), presumptive evidence was obtained for the presence of galactose, rhamnose, and 3-methyl galactose. This result was confirmed by the separation of the sugars on a column of cellulose, *n*-butanol–ethanol–water being used as the mobile phase (*idem, ibid.*, 1949, 2511), which led to the isolation of pure crystalline specimens of D-galactose, 3-methyl D-galactose, and L-rhamnose. Traces of at least three other sugars were detected, two of which appear to be glucose and fucose. 3-Methyl D-galactose isolated from slippery elm mucilage was identical in all respects with a synthetic specimen kindly supplied by Professor T. Reichstein. A preliminary account of these results has been given elsewhere (Hirst, Hough, and Jones, *Nature*, 1950, **165**, 34). 3-Methyl D-galactose has not been encountered hitherto in any natural product, and it is of interest to note the relation to the cardiac glycosides in which 3-methyl D-fucose (digitalose), 3-methyl 2-deoxy-D-allose (cymarose), and 3-methyl 2 : 6-dideoxy-D-allose (olleandreose) have been detected (cf. Elderfield, *Adv. Carbohydrate Chem.*, 1945, **1**, 147). It is noteworthy that the methylated sugars encountered so far in Nature are all of the 3-methyl type, thus raising an important phytochemical problem. In the case of the uronic acids, however, only one natural methyl derivative has so far been detected, namely, 4-methyl D-glucuronic acid in Mesquite gum (White, *J. Amer. Chem. Soc.*, 1948, **70**, 367).

The provisional formula for the general structure advanced by Gill, Hirst, and Jones (*loc. cit.*) for the carbohydrate portion of slippery elm mucilage still holds and it remains to determine which galactose residues are substituted on $C_{(3)}$ by methoxyl groups. A consideration of the analytical data for the purified mucilage, in conjunction with the results obtained for the hydrolysis products of the gum, indicates that the following monosaccharide residues are present, approximately in the proportions indicated: D-galactose (1 part), 3-methyl D-galactose (1 part), L-rhamnose (2 parts), and D-galacturonic acid (2 parts). A polysaccharide built up of these residues in the proportions indicated would contain 3·2% of methoxyl groups.

Experimental.

Hydrolysis of the Purified Polysaccharide.—The mucilage was extracted from slippery elm bark and purified by the method described in Part I (*loc. cit.*). The purified material had $[\alpha]_D^{20}$ +65° in water (*c*, 0·87) [Found: N, 0·5; sulphated ash, 1·9; OMe, 3·3%; equiv., 452 (by titration with alkali)]. The polysaccharide (5 g.) was dissolved in N-sulphuric acid (50 ml.) and heated in the boiling-water bath for 9 hours. The solution was then cooled, neutralised with a slurry of barium carbonate, and filtered, and the filtrate evaporated under reduced pressure. The residue was extracted with boiling methanol (4 × 150 ml.), and the extracts were combined and evaporated under reduced pressure to a thick syrup (*A*) (1·5 g.). The insoluble barium salts (*B*) were collected and dried *in vacuo* over phosphoric oxide at 60° (yield, 3·6 g.) (Found: Ba, 25·3; OMe, 2·2%).

Separation of the Mixture of Sugars. (A).—The syrup (*A*) (1·2 g.) was separated on a column of cellulose, *n*-butanol (95%)–ethanol (5%) nearly saturated with water being used as the mobile phase. After an examination of small portions of the eluate on the paper chromatogram, the eluate was divided in such a manner as to lead to the highest possible recovery of each component sugar. The solvent was removed by distillation under reduced pressure and the following fractions were obtained: Fraction I (0·17 g.) had R_G 0·30 and when crystallised gave L-rhamnose hydrate, m. p. 98—100°, $[\alpha]_D$ +9° (*c*, 1·2). Fraction II (0·005 g.) showed $[\alpha]_D$ +14° ± 10° (*c*, 0·2), and moved to the same position on the paper chromatogram as fucose; it also showed the same colour reactions when the paper chromatogram was sprayed with acidic solutions of diphenylamine, α-naphthylamine, or aniline and heated. This evidence is only indicative, however, and further evidence will be necessary for its conclusive identification. Fraction III (0·168 g.), R_G 0·17, crystallised from acetone–methanol, giving 3-methyl D-galactose, m. p. and mixed m. p. 140—141°, $[\alpha]_D^{18}$ +139° (10 minutes; *c*, 0·2 in water) ⟶ +86° (20 hours; constant value), $[\alpha]_D^{18}$ +62° (initial value; *c*, 0·2 in 4% methanolic hydrogen chloride) ⟶ −43° (16 hours; constant value) (Found: C, 43·3; H, 7·6; OMe, 15·2. Calc. for $C_7H_{14}O_6$: C, 43·3; H, 7·2; OMe,

16·0%); an *X*-ray powder photograph of the crystals was identical with that of a known specimen of 3-methyl D-galactose. Fraction IV (0·082 g.) showed $[\alpha]_D$ +70° (*c*, 1·6 in water) and consisted of a mixture of 3-methyl galactose (R_G 0·17) and an unidentified sugar (R_G 0·135). Fraction V (0·023 g.) showed $[\alpha]_D$ +33° (*c*, 0·9 in water). The rate of movement (R_G 0·135) on the paper chromatogram, and colour reactions with the specific spray reagents described above were not sufficient to characterise the sugar. Fraction VI (0·010 g.) showed $[\alpha]_D$ +33° (*c*, 0·4 in water), moved to the same position on the paper chromatogram as glucose (R_G 0·095), and gave an osazone (m. p. 204—205°) with a crystalline form typical of glucosazone. Fraction VII (0·07 g.) contained galactose (R_G 0·07) and traces of glucose (R_G 0·095). The syrup was dissolved in a little methanol and, on being kept, gave crystals of D-galactose {m. p. and mixed m. p. 166°; $[\alpha]_D$ +81·0° (equilibrium value; *c*, 0·5 in water); R_G 0·07}. Fraction VIII (0·368 g.) crystallised spontaneously to give D-galactose {m. p. and mixed m. p. 164—165°; $[\alpha]_D$ +81·8° (equilibrium value; *c*, 0·98 in water); R_G 0·07}.

Examination of the Barium Salts (B).—A portion was hydrolysed in 2N-sulphuric acid in a sealed tube immersed in a boiling-water bath. After neutralisation with barium carbonate, the solution was filtered, the filtrate evaporated, and the residue extracted with boiling methanol. The methanol extract was evaporated to a syrup which was examined on the paper chromatogram amd observed to contain mainly rhamnose (R_G 0·30), with only a small quantity of galactose (R_G 0·07) and 3-methyl galactose (R_G 0·17). The syrup crystallised overnight giving L-rhamnose hydrate {$[\alpha]_D$ +9° (*c*, 0·98 in water); m. p. 98—100°}. Another portion of the barium salts (*B*) was treated with Amberlite I.R. 100 and when free from barium the solution was evaporated to a syrup. The syrup was separated on the paper chromatogram, *n*-butanol (50 parts), acetic acid (25 parts), and water (25 parts) being used as the mobile phase, and developed with *p*-anisidine hydrochloride. Spots corresponding to rhamnose, 3-methyl galactose, galactose, galacturonic acid, and galacturonosidorhamnose were obtained.

Quantitative Examination of the Products of the Mucilage.—The dry, ash-free mucilage (269·7 mg.) was hydrolysed with 2N-sulphuric acid in a sealed tube immersed in a boiling-water bath for 12 hours. The tube was cooled and opened, and the contents added to ribose (68 mg.). The solution was neutralised with barium carbonate and filtered, and the filtrate evaporated to a syrup. The sugars were separated by paper chromatography and estimated by oxidation with periodate solution. The assumption was made that 3-methyl galactose is oxidised by this reagent in the same manner as 3-methyl glucose (Found: galactose, 0·544 mg.; 3-methyl galactose, 0·825 mg.; ribose, 0·625 mg.; rhamnose, 0·714 mg.). These figures correspond to the presence of 21·6% galactose (as $C_6H_{12}O_6$), 26·8% of 3-methyl galactose (as $C_7H_{14}O_6$), and 25·2% of rhamnose (as $C_6H_{12}O_5$) in the mucilage. Hydrolysis of the galacturonosido-rhamnoside linkage is difficult and the rhamnose figure is low, probably because of incomplete hydrolysis (cf. Gill, Hirst, and Jones, *loc. cit.*).

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THE UNIVERSITY, BRISTOL.
THE UNIVERSITY, EDINBURGH.

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73. *The Action of Hydrazine on Benzoxazolones.*

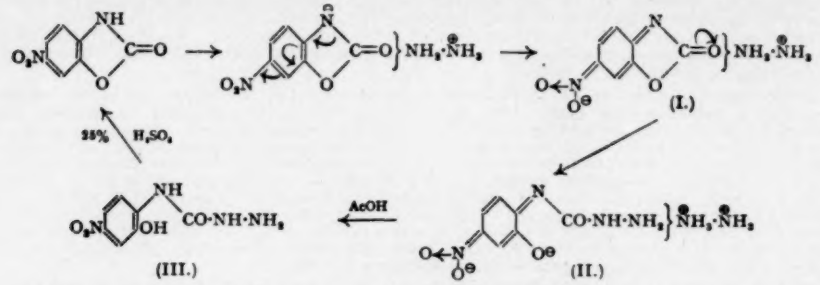
By J. D. BOWER and F. F. STEPHENS.

Reaction of 6-nitrobenzoxazolone with alcoholic hydrazine hydrate gives a hydrazine salt which easily breaks down into 4-(2-hydroxy-4-nitrophenyl)-semicarbazide. In this reaction benzoxazolone gives 4-*o*-hydroxyphenyl-semicarbazide, and 2-mercaptobenzoxazoles give *o*-aminophenols.

2-AMINO-5-NITROPHENOL is best obtained by the action of ammonia on 6-nitrobenzoxazolone in an autoclave (F.I.A.T. Final Report No. 1313, p. 203). It seemed possible that ring opening could be achieved more simply by treatment with hydrazine (cf. Boggust and Cocker, *J.*, 1949, 355) although it is reported (D.R.-P. 614,327; *Chem. Centr.*, 1935, II, 2583) that this reaction yields 2-hydrazinobenzazoles.

6-Nitrobenzoxazolone in hot alcoholic hydrazine hydrate gave an unstable, bright red, crystalline solid, $C_7H_{12}O_4N_6$, changed by dilute acetic acid into a stable, bright yellow compound, $C_7H_8O_4N_4$, the latter being obtained directly from 6-nitrobenzoxazolone and hydrazine in aqueous solution. When either compound was heated with 25% sulphuric acid 6-nitrobenzoxazolone together with hydrazine sulphate was obtained. Clearly the red compound was a hydrazine salt of the yellow one and reactions of the latter led us to the opinion that it was 4-(*o*-hydroxy-*p*-nitrophenyl)semicarbazide (III) (see Experimental). It is probable that the reactions described above accord with the annexed scheme: the mesomeric *aci*-nitro-form

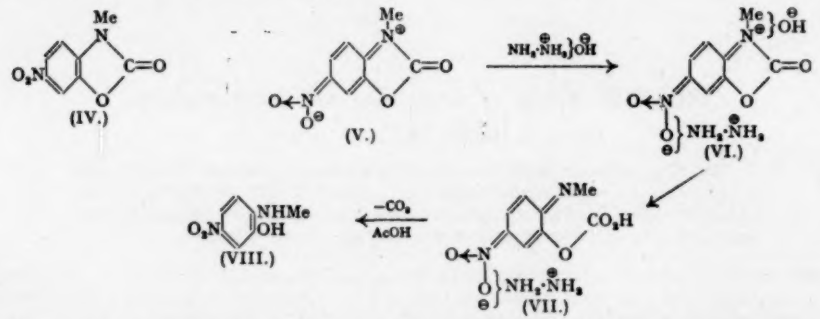
(I) of the initial hydrazine salt reacts further with hydrazine to give the unstable red salt (II) and thence the yellow compound (III). The final cyclisation of the semicarbazide to the benzoxazolone is supported by the statement (Beilstein, " Handbuch der organischen Chemie," 4th Edn., XIII, p. 391) that 2-hydroxy-4-nitrophenylurea is converted into 6-nitrobenzoxazolone by hot mineral acids [see also Darapsky (*J. pr. Chem.*, 1936, **147**, 145) on the opening of lactone



rings with hydrazine]. Finally, the semicarbazide (III) was prepared by reaction of 2-hydroxy-4-nitrophenylurethane (Desai, Hunter, and Khalidi, *J.*, 1938, 327) with hydrazine hydrate and was identical with the above-mentioned yellow compound.

Application of this reaction to benzoxazolone itself produced 4-*o*-hydroxyphenylsemicarbazide, also synthesised from *o*-hydroxyphenylurethane (Groenvik, *Bull. Soc. chim.*, 1876, **25**, 177; see also Raiford *et al.*, *J. Org. Chem.*, 1939, **4**, 207; 1941, **6**, 858) and hydrazine.

In order to prevent the initial formation of a negative charge on the ring-nitrogen atom the reaction was repeated with 3-methyl-6-nitrobenzoxazolone. Attempts to prepare this compound by methylation of 6-nitrobenzoxazolone with methyl sulphate and alkali were unsuccessful. Benzoxazolone was easily methylated under these conditions (cf. Desai, Hunter, *et al.*, *J.*, 1934, 1186) and nitration of the resulting 3-methyl compound gave the desired substance. When this was heated with alcoholic hydrazine hydrate 2-methylamino-5-nitrophenol (VIII) was obtained. The failure to form a semicarbazide in this reaction is readily intelligible if reaction proceeded as shown :



(IV) reacts with hydrazine hydrate as if it possesses the zwitterion resonance form (V) to produce the *aci*-nitro-quaternary hydroxide (VI) and this undergoes a transformation, analogous to ψ-base formation or the ring opening of pyridinium compounds with alkali, leading to the unstable carbonate (VII) and thence (VIII).

The mechanisms suggested above require as an essential preliminary the formation of either a negative or a positive charge on the ring-nitrogen atom. In the case of 3-methylbenzoxazolone this would not be possible and it was deduced that this substance should remain unchanged on refluxing with hydrazine hydrate. This was found to be the case.

Reaction of 2-mercapto-6-nitrobenzoxazole (Desai, Hunter, and Khalidi, *J.*, 1938, 327) with hydrazine hydrate gave hydrogen sulphide, ammonia (see Boggust and Cocker, *loc. cit.*),

and 2-amino-5-nitrophenol. Under these conditions 2-mercaptobenzoxazole gave hydrogen sulphide and *o*-aminophenol, together with an unidentified solid. Methylation of 2-mercapto-6-nitrobenzoxazole by methyl sulphate and alkali proceeded very easily (contrast the behaviour of 6-nitrobenzoxazolone), and the product (2-methylthio-6-nitrobenzoxazole) reacted with hydrazine to give methanethiol and 2-amino-5-nitrophenol. It is clear that in these mercapto-compounds hydrogenolysis of the heterocyclic carbon–sulphur bond is followed by the oxidation-reduction reaction described by Boggust and Cocker (*loc. cit.*).

Experimental.

Hydrazine salt of 4-(2-*hydroxy*-4-*nitrophenyl*)*semicarbazide.*—6-Nitrobenzoxazolone (1 g.), hydrazine hydrate (2 ml.; 100%), and ethanol (7 ml.) were boiled together under reflux for a few minutes, the mixture becoming nearly solid with bright red crystals (1·25 g.), m. p. 235° (decomp.). The solid was filtered off, washed with anhydrous ether, and dried in a vacuum-desiccator over phosphoric oxide [Found: C, 34·6; H, 5·25; N, 34·4; N_2H_4 (determined, after warming the compound with 4N-HCl) (Kolthoff, *J. Amer. Chem. Soc.*, 1924, **46**, 2009), 25·4. $C_7H_{11}O_4N_5$ requires C, 34·4; H, 4·9; N, 34·4; N_2H_4, 26·2%].

4-(2-*Hydroxy*-4-*nitrophenyl*)*semicarbazide.*—(*a*) To the above hydrazine salt (1·25 g.) were added acetic acid (5 ml.), then water (10 ml.), and the bright yellow semicarbazide (1·06 g.), m. p. 226—228°, was removed and dried. Recrystallisation from benzonitrile did not change the m. p. The *semicarbazide* was soluble in dilute alkali and dilute mineral acids, in alcoholic solution gave an olive-green colour with ferric chloride (cf. Semper and Lichtenstadt, *Annalen*, 1913, **400**, 326, for the case of 2-hydroxy-4-nitrophenylurea), and reduced both Fehling's and ammoniacal silver nitrate solutions (Found: C, 40·0; H, 3·9; N, 26·5. $C_7H_8O_4N_4$ requires C, 39·6; H, 3·8; N, 26·4%). The 1-*p*-*nitrobenzylidene* derivative, m. p. 267°, was recrystallised from aqueous pyridine (Found: C, 49·4; H, 3·7; N, 20·7. $C_{14}H_{11}O_6N_5$ requires C, 48·7; H, 3·2; N, 20·3%).

(*b*) 2-Hydroxy-4-nitrophenylurethane (1 g.), hydrazine hydrate (5 ml.; 100%), and ethanol (10 ml.) were refluxed for 7 hours. The mixture formed a bright red solution which was diluted and neutralised with 50% acetic acid to give yellow needles (0·5 g.), m. p. 226—228° alone or when mixed with the product from (*a*).

(*c*) 6-Nitrobenzoxazolone (1 g.) was boiled for 3 minutes with hydrazine hydrate (1·75 ml.; 90%) in water (6·5 ml.). The solution was cooled and filtered and the precipitate washed with water. The yield of yellow crystals, m. p. 228°, was 1·05 g.

6-*Nitrobenzoxazolone.*—The above semicarbazide (1 g.) was boiled under reflux with sulphuric acid (50 ml.; 25%) for 30 minutes. At first the semicarbazide dissolved but after 15 minutes a white precipitate appeared. Dilution with water gave 6-nitrobenzoxazolone (0·8 g.), m. p. 248—249°, alone or mixed with 6-nitrobenzoxazolone.

3-*Methylbenzoxazolone.*—Benzoxazolone (6·7 g.) was dissolved in 2N-sodium hydroxide solution (60 ml.) and methylated by the addition of two successive portions of methyl sulphate (each 5 ml.), the mixture being kept alkaline to phenolphthalein. The precipitated methyl compound (5 g.) was recrystallised from ligroin, giving white crystals, m. p. 85—85·5° (Found: N, 9·3. Calc. for $C_8H_7O_2N$: N, 9·4%).

3-*Methyl*-6-*nitrobenzoxazolone.*—3-Methylbenzoxazolone (4·5 g.) was added to concentrated nitric acid (35 ml.; *d* 1·42) at 90° and the mixture kept at this temperature for 15 minutes. The *product* was isolated by dilution and recrystallised from ethanol as white needles (4·7 g.), m. p. 186—187° (Found: N, 14·2. $C_8H_6O_4N_2$ requires N, 14·4%).

2-*Methylamino*-5-*nitrophenol.*—3-Methyl-6-nitrobenzoxazolone (1 g.) was refluxed with ethanol (7 ml.) and hydrazine hydrate (2 ml.; 100%) for 4 hours. The mixture was poured into water (50 ml.) and acidified with acetic acid, and the bright orange *phenol* (0·65 g.) collected. Recrystallisation from water gave orange needles (0·5 g.), m. p. 188° (Found: N, 16·8. $C_7H_8O_3N_2$ requires N, 16·7%).

4-*o*-*Hydroxyphenylsemicarbazide.*—(*a*) Benzoxazolone (2 g.), ethanol (16 ml.), and hydrazine hydrate (4 ml.; 100%) were boiled under reflux for 2·5 hours. The mixture was poured into water (50 ml.) and acidified with acetic acid, giving the *semicarbazide* (2 g.), m. p. 156°. Recrystallisation from water (charcoal) gave blunt white needles (becoming pale yellow) (1·3 g.), m. p. 156° (Found: C, 51·0; H, 5·9; N, 25·3. $C_7H_9O_3N_3$ requires C, 50·3; H, 5·39; N, 25·1%). The compound gave a cherry-red colour in Smith's test (*Analyst*, 1935, **60**, 171) (2-hydrazinobenzoxazole gave a yellow colour), was soluble in cold dilute sodium hydroxide solution, and gave a red-brown colour with ferric chloride.

(*b*) *o*-Hydroxyphenylurethane (1 g.), ethanol (3·5 ml.), and hydrazine hydrate (2·5 ml.; 100%) were refluxed for 7 hours, and the product was isolated as described under (*a*), giving white needles (0·5 g.), m. p. 156° not depressed on admixture with the above product. When the compound was heated with 25% sulphuric acid, benzoxazolone (m. p. 140—141° alone or mixed with pure benzoxazolone) was obtained.

2-*Methylthio*-6-*nitrobenzoxazolone.*—2-Mercapto-6-nitrobenzoxazole (1 g.), suspended in sodium hydroxide solution (16 ml.; 2N.), was treated with two (1·5-ml.) portions of methyl sulphate, the mixture being kept alkaline to phenolphthalein. After 15 minutes, 2-*methylthio*-6-*nitrobenzoxazole* (0·83 g.) was removed, washed with water, and recrystallised from ethanol as pale yellow needles, m. p. 124° (Found: N, 13·6. $C_8H_6O_3N_2S$ requires N, 13·3%).

2-*Amino*-5-*nitrophenol.*—2-Mercapto-6-nitrobenzoxazole (1 g.) was refluxed with ethanol (8 ml.) and hydrazine hydrate (2 ml.; 100%) for 2·5 hours (by this time the evolution of hydrogen sulphide had

stopped and ammonia was being evolved). The mixture was cooled, diluted, neutralised with acetic acid, and extracted with ether, to give 2-amino-5-nitrophenol (0·55 g.). Recrystallisation from water gave orange needles, m. p. 207—208° alone or mixed with a pure specimen (Found: N, 18·9. Calc. for $C_6H_6O_3N_2$: N, 18·2%).

2-Methylthio-6-nitrobenzoxazole (1 g.) reacted under the conditions described above, to give methanethiol and 2-amino-5-nitrophenol (0·5 g.), m. p. 207—208°. 2-Mercaptobenzoxazole (1 g.) gave *o*-aminophenol (0·6 g.) and an unidentified solid (0·16 g.), m. p. 248°.

We thank the Analytical Division for all analyses, and Mr. J. A. Coombs for experimental assistance.

FISONS RESEARCH LABORATORIES,
LOUGHBOROUGH, LEICS.

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74. *An Investigation of the Reactions of Phenyl-lithium with Some Methylpyrimidines.*

By T. D. HEYES and JOHN C. ROBERTS.

The reactions of phenyl-lithium with some 2- and 4-methylpyrimidines have been investigated. The broad mechanisms of the reactions have been deduced from the nature of the end-products. There were observed three main types of reaction involving, respectively, the initial formation of (i) an addition compound which, on hydrolysis, yielded a dihydro-phenyl derivative of the original pyrimidine; (ii) an addition compound which, under the experimental conditions, spontaneously split off lithium hydride to give a phenyl derivative; and (iii) a pyrimidylmethyl-lithium which reacted normally with an alkyl halide. In one case a dimerised pyrimidylmethyl was obtained, in poor yield, as the sole product.

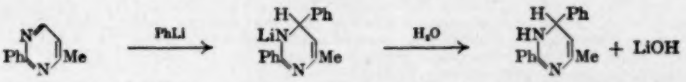
OTHER work in progress in this laboratory necessitated the development of a synthesis for a pyrimidine containing a long-chain aliphatic substituent. This paper records investigations undertaken in the expectation that, by the reaction of phenyl-lithium with methylpyrimidines, pyrimidylmethyl-lithium compounds would be formed, which, on treatment with appropriate alkyl halides, would lead to the desired products.

This expectation was based on the following considerations. A close similarity between the reactivity of methyl groups in the 2- and the 4-positions of the pyridine nucleus and of methyl groups in the 2- and the 4-positions of the pyrimidine nucleus is indicated by the ease with which both these types of compounds form styryl derivatives (Gabriel and Colman, *Ber.*, 1903, **36**, 3383; Ochiai and Yanai, *J. Pharm. Soc. Japan*, 1938, **58**, 76; *Chem. Zentr.*, 1938, II, 4242). Theoretical grounds for this similarity have been suggested previously by one of us (Roberts, *Chem. and Ind.*, 1947, **66**, 658). It seemed, therefore, reasonable to expect that, in reactions with phenyl-lithium, the methyl groups of 2- and 4-methylpyrimidines would behave similarly to those of 2-methyl-pyridine and -quinoline which are known to give 2-pyridyl- (Ziegler and Zeiser, *Annalen*, 1931, **485**, 174) and 2-quinolyl-methyl-lithium (Graef, Fredericksen, and Burger, *J. Org. Chem.*, 1946, **11**, 257). The last two compounds have been used as intermediates in chain-lengthening processes, as they react with alkyl halides in the normal manner (Bergmann and Rosenthal, *J. pr. Chem.*, 1932, **135**, 267; Graef *et al.*, *loc. cit.*).

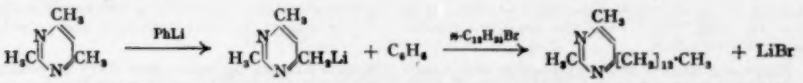
Reactions between phenyl-lithium and 2-methyl-, 4-methyl-, 4-methyl-2-phenyl-, 4-methyl-2 : 6-diphenyl-, and 2 : 4 : 6-trimethyl-pyrimidine were carried out. When the initial reaction was complete, an alkyl halide (generally *n*-dodecyl bromide) was added to react with any pyrimidylmethyl-lithium compound which had been formed, and the final products were isolated and their structures established. In this connection a reaction due to Wolff (*Ber.*, 1892, **25**, 3033) and Byk (*ibid.*, 1903, **36**, 1923) proved particularly useful. Reduction of the pyrimidine or dihydropyrimidine by sodium and alcohol yielded a hexahydropyrimidine which, on acid hydrolysis, underwent ring fission, producing an aldehyde of which the alkyl or aryl group was the grouping originally attached to the 2-position.

A number of different mechanisms were found. 4-Methyl-2-phenylpyrimidine gave 1 : 6-dihydro-4-methyl-2 : 6-diphenylpyrimidine in good yield as the sole product. The structure of this compound follows from the following facts: (i) it yielded a positive Liebermann reaction,

indicating the presence of a secondary amino-group, and (ii) on oxidation with potassium permanganate in acetone solution it gave the known 4-methyl-2 : 6-diphenylpyrimidine. It was concluded that the reaction had occurred thus :



Pyridine is known to undergo an analogous reaction (Ziegler and Zeiser, *Ber.*, 1930, **63**, 1847; *Annalen*, 1931, **485**, 174). 4-Methylpyrimidine yielded a mixture of 4-methyl-2-phenylpyrimidine and 4-methyl-6-phenylpyrimidine, as shown by (i) analysis, (ii) separation and identification of the 6-phenyl isomer, and (iii) reduction of the mixture with sodium and alcohol, followed by acid hydrolysis, whereupon formaldehyde and benzaldehyde were obtained. It was not possible to separate the 2-phenyl isomer in a pure state. The nature of the products of this reaction indicates that addition of phenyl-lithium to the 1 : 6 or 1 : 2 positions of the pyrimidine nucleus takes place initially and that this is then followed by fission of lithium hydride from the adduct. [The pyridine–phenyl-lithium addition product undergoes a similar reaction when heated (Ziegler and Zeiser, *locc. cit.*)]. Owing to the difficulties of the single available synthesis, only a small quantity of 2-methylpyrimidine was prepared. This gave a product, insufficient in quantity for purification as such, which yielded with picric acid the picrate of either 2-methyl-4-phenyl-, 3 : 4-dihydro-2-methyl-4-phenyl-, or 1 : 2-dihydro-2 methyl-2-phenyl-pyrimidine. The mechanism of this reaction is therefore similar to one or other of the two reactions mentioned above. Treatment of 2 : 4 : 6-trimethylpyrimidine with phenyl-lithium followed by *n*-dodecyl bromide gave a good yield of 2 : 6-dimethyl-4-*n*-tridecylpyrimidine, thus indicating the production of 2 : 6-dimethyl-4-pyrimidylmethyl-lithium as an intermediate product :



That the 2-methyl group had not been attacked was shown by the production of acetaldehyde alone when the product was reduced and hydrolysed. A much smaller quantity of 2-methyl-4 : 6-di-*n*-tridecylpyrimidine was obtained as a by-product. When, however, 4-methyl-2 : 6-diphenylpyrimidine was similarly treated, a large amount of unchanged starting material was obtained together with a very small quantity of *s*-di-(2 : 6-diphenyl-4-pyrimidyl)ethane which had possibly been produced by the dimerisation of two 2 : 6-diphenylpyrimidylmethyl radicals.

Hence of all the cases examined, the expected chain-lengthening process occurred only with 2 : 4 : 6-trimethylpyrimidine. In this instance it had been expected that the 2-methyl group would be attacked preferentially, since this group is more reactive than the 4- and the 6-methyl group towards benzaldehyde (Ochiai and Yanai, *loc. cit.*), whereas in fact the 4- or the 6-methyl group was attacked to the exclusion of the 2-methyl group. Finally, it is noteworthy that in those cases (except possibly that of 2-methylpyrimidine) in which the 2- or the 6-position in the pyrimidine ring was vacant, a phenyl group entered the ring at one of these points and the methyl group was not attacked. (The reactivity of the methyl groups of 4-methyl-2-phenyl- and 4-methyl-2 : 6-diphenyl-pyrimidine in an aldol type of reaction was confirmed by the preparation of 2-phenyl-4-styryl- and of 2 : 6-diphenyl-4-styryl-pyrimidine. Similar derivatives of the other methylpyrimidines mentioned in this paper, with the exception of 2-methylpyrimidine, have been prepared previously by other workers.)

Experimental.

Characterisation of the Substituent in the 2-Position of the Pyrimidine or Dihydropyrimidine Nucleus.—A solution of the base (0·2 g.) in dry ethanol (5 c.c.) was boiled under reflux on the water-bath. Small pieces of sodium (1·0 g. in all) were added rapidly through the condenser. When the reaction abated, more dry ethanol (10 c.c.) was added and heating continued until all the solid had dissolved. Concentrated hydrochloric acid (10 c.c.), diluted with water (30 c.c.), was then added and the resulting solution steam-distilled. The distillate was mixed with an excess of a 0·33% solution of 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid, and the precipitated 2 : 4-dinitrophenylhydrazone was recrystallised from a suitable solvent and identified by its m. p., alone and after admixture with an authentic specimen.

Reaction between 4-Methyl-2-phenylpyrimidine and Phenyl-lithium. 1 : 6-Dihydro-4-methyl-2 : 6-diphenylpyrimidine.—A phenyl-lithium solution was prepared from bromobenzene (4·7 g., 1·0 mol.),

lithium chips (0·43 g., 2·03 atoms), and dry ether (50 c.c.) under nitrogen. 4-Methyl-2-phenylpyrimidine (5·12 g., 1·06 mols.), prepared by Schmidt's method (*Ber.*, 1902, **35**, 1575), dissolved in dry ether (20 c.c.), was added slowly and with stirring. After 15 minutes, a solution of *n*-dodecyl bromide (6·97 g., 0·94 mol.) in dry ether (20 c.c.) was added slowly. The mixture was heated under reflux, with stirring, for 1 hour and was then cooled and shaken with water. The separated ethereal layer was extracted with N-hydrochloric acid, the extract was made alkaline, and the resulting yellow crystalline precipitate filtered off, washed with water, dried (2·8 g.), and recrystallised from acetone. 1 : 6-*Dihydro*-4-*methyl*-2 : 6-*diphenylpyrimidine* forms pale-yellow irregular plates, m. p. 142° (Found : C, 82·9; H, 6·45; N, 11·2. $C_{17}H_{16}N_2$ requires C, 82·2; H, 6·5; N, 11·3%).

Oxidation of 1 : 6-*Dihydro*-4-*methyl*-2 : 6-*diphenylpyrimidine to* 4-*Methyl*-2 : 6-*diphenylpyrimidine.*—The base (0·4 g.) was dissolved in acetone (10 c.c.) and finely powdered potassium permanganate (0·17 g.) was added slowly with shaking and cooling, the temperature being kept below 30°. The precipitated manganese dioxide was filtered off and washed well with acetone. The acetone was evaporated from the combined filtrate and washings; the residual oil (0·35 g.), when scratched, solidified. The solid, after crystallisation from ethanol, formed hexagonal prisms, m. p. 93—94° alone or mixed with an authentic specimen of 4-methyl-2 : 6-diphenylpyrimidine, prepared by Asahina and Kuroda's method (*Ber.*, 1914, **47**, 1818).

Reaction between 4-*Methylpyrimidine and Phenyl-lithium.* 4-*Methyl*-2-*phenyl- and* 4-*Methyl*-6-*phenyl-pyrimidine.*—4-Methylpyrimidine (9·6 g., 1·02 mols.) [prepared by Gabriel and Coleman's method (*Ber.*, 1899, **32**, 1534)], dissolved in dry ether (20 c.c.), was added slowly and with stirring to a solution of phenyl-lithium (8·4 g., 1·0 mol.) in dry ether (100 c.c.). After 15 minutes, *n*-dodecyl bromide (21·7 g., 0·9 mol.) was added and the reaction carried out as before. The reaction mixture was shaken with water and the ethereal layer was separated. This was extracted with N-hydrochloric acid, the extract made alkaline, and the resulting emulsion extracted with ether; the extract was dried (KOH) and filtered, the solvent removed, and the residue was distilled *in vacuo*, the fraction, b. p. 142—150°/11 mm. (2·0 g.), being collected (Found : C, 77·8; H, 5·8; N, 16·2. Calc. for $C_{11}H_{10}N_2$: C, 77·6; H, 5·9; N, 16·5%). Reduction and hydrolysis of this material gave a mixture of benzaldehyde and formaldehyde (the 2 : 4-dinitrophenylhydrazones of these aldehydes were separated by fractional crystallisation from absolute ethanol and identified in the usual way). The distillate, after 2 days at room temperature, had partially solidified. The solid was filtered off and crystallised from light petroleum (b. p. 40—60°) giving colourless, hexagonal plates (1 g.), m. p. 48° alone or when mixed with an authentic specimen of 4-methyl-6-phenylpyrimidine, prepared by Merkatz's method (*Ber.*, 1919, **52**, 880). Thus, the mixture contained the two isomers, 4-methyl-2-phenyl- and 4-methyl-6-phenyl-pyrimidine.

Reaction between 2-*Methylpyrimidine and Phenyl-lithium.*—The faintly yellow gum (0·26 g.) obtained from 2-methylpyrimidine (0·4 g.) in a manner analogous to that described for the 4-methyl isomer could not be crystallised. A solution of the gum in a little 2N-hydrochloric acid was mixed with an excess of a saturated aqueous solution of picric acid. The picrate, which was immediately precipitated, was filtered off and extracted with hot benzene, leaving a tarry residue. When the benzene solution was cooled, crystals formed which were recrystallised from 2-ethoxyethanol; the *picrate* of 2-methyl-4-phenyl-, or 3 : 4-dihydro-2-methyl-4-phenyl- or 1 : 2-dihydro-2-methyl-2-phenyl-pyrimidine crystallised in yellow needles, m. p. 205° (decomp.) (Found : N, 17·6. $C_{17}H_{13}O_7N_5$ requires N, 17·54. $C_{17}H_{13}N_5O_7$ requires N, 17·46%).

Reaction between 2 : 4 : 6-*Trimethylpyrimidine and Phenyl-lithium.* 2 : 6-*Dimethyl*-4-*n-tridecyl-pyrimidine and* 2-*Methyl*-4 : 6-*di-n-tridecylpyrimidine.*—2 : 4 : 6-Trimethylpyrimidine (14·64 g., 1·0 mol.) [prepared by Bowman's method (*J.*, 1937, 494)], in dry ether (25 c.c.), was added slowly, with stirring and cooling, to a solution of phenyl-lithium (10·28 g., 1·0 mol.) in dry ether (80 c.c.). After being heated under reflux and stirred for 15 minutes, the mixture, which contained a sticky mass of 2 : 6-dimethyl-4-pyrimidylmethyl-lithium, was cooled. *n*-Dodecyl bromide (28·6 g., 0·99 mol.) was added slowly, with stirring and cooling, whereupon all the solid dissolved. The rest of the reaction was carried out and the product extracted as before. The crude product (15 g.) was distilled *in vacuo*; two fractions were obtained [(i) b. p. 144°/0·1 mm., and (ii) b. p. 194°/0·05 mm.] and both solidified on cooling. The first fraction was dissolved in light petroleum (b. p. 60—80°), and the solution saturated with hydrogen chloride. The precipitated hydrochloride was recrystallised from light petroleum (b. p. 60—80°) and formed needles, m. p. 80°. It was dissolved in water, the aqueous solution made alkaline, the emulsion so formed extracted with ether, the extract dried ($MgSO_4$), the ether distilled off, and the residue distilled under reduced pressure (b. p. 144°/0·1 mm.), giving 2 : 6-*dimethyl*-4-*n-tridecylpyrimidine* (11 g.), which crystallised in needles, m. p. 23° (Found : C, 78·4; H, 12·0; N, 9·4. $C_{18}H_{34}N_2$ requires C, 78·7; H, 11·8; N, 9·65%).

The second fraction was recrystallised from absolute ethanol; 2-*methyl*-4 : 6-*di*-n-*tridecylpyrimidine* (1 g.) was obtained in needles, m. p. 29—30° (Found : C, 81·1; H, 12·8; N, 6·2. $C_{31}H_{58}N_2$ requires C, 81·1; H, 12·7; N, 6·1%).

On reduction and hydrolysis both fractions gave acetaldehyde.

Reaction between 4-*Methyl*-2 : 6-*diphenylpyrimidine and Phenyl-lithium.* s-*Di*-(2 : 6-*diphenyl*-4-*pyrimidyl*)*ethane.*—4-Methyl-2 : 6-diphenylpyrimidine (5·0 g., 1·0 mol.), dissolved in dry ether (7·5 c.c.), was added slowly and with stirring to a solution of phenyl-lithium (1·68 g., 1·0 mol.) in dry ether (75 c.c.). After the reaction mixture had been stirred and heated under reflux for 30 minutes, *n*-hexyl bromide (3·35 g., 0·99 mol.) was added, slowly and with stirring. The rest of the procedure was as already described. When the reaction mixture was shaken with 2N-hydrochloric acid a white solid separated which was soluble in neither the acid nor the ether. This was filtered off and the filtrate treated as before. A crystalline material (2·3 g.) was obtained which melted at 93—94°, alone or when

mixed with 4-methyl-2 : 6-diphenylpyrimidine and hence was unchanged starting material. The solid which was insoluble in hydrochloric acid and in ether was dissolved in hot pyridine from which, on cooling, *s-di-(2 : 6-diphenyl-4-pyrimidyl)ethane* crystallised as needles, m. p. 226° [Found : C, 82·9; H, 5·5; N, 11·6%; *M* (Micro-Rast), 415. $C_{34}H_{26}N_4$ requires C, 83·2; H, 5·3; N, 11·4%; *M*, 491].

2-Phenyl-4-styrylpyrimidine.—A mixture of 4-methyl-2-phenylpyrimidine (4 g., 1 mol.) and acetic anhydride (1·1 c.c.) was added slowly, during 10 minutes, to boiling benzaldehyde (4·9 c.c., 2 mols.) (cf. Shaw and Wagstaff, *J.*, 1933, 77). After 6 hours' heating, the product was distilled in steam, and the tarry residue was extracted with hot 5N-hydrochloric acid. After the hot solution had been filtered, crystals of the base hydrochloride were deposited. These were recrystallised from 2N-hydrochloric acid (charcoal) as long, fine needles, m. p. 201°. A hot solution of the hydrochloride in 2N-hydrochloric acid was made alkaline, and the emulsion, so formed, was extracted with ether, the extract dried (Na_2SO_4), the solvent evaporated, and the residual oil crystallised first from ethanol and then from 2-ethoxyethanol. *2-Phenyl-4-styrylpyrimidine* (0·3 g.) crystallised as needles, m. p. 109° (Found : C, 83·9; H, 5·45; N, 11·2. $C_{18}H_{14}N_2$ requires C, 83·7; H, 5·5; N, 10·8%).

2 : 6-Diphenyl-4-styrylpyrimidine.—4-Methyl-2 : 6-diphenylpyrimidine (4·0 g., 1 mol.), suspended in an excess of acetic anhydride (10 c.c.), was allowed to react with benzaldehyde (3·5 g., 2 mols.) as before. The heating was continued for 12 hours and the reaction mixture distilled in steam. The residue was extracted with 5N-hydrochloric acid (to remove unchanged starting material) and was then dissolved in ethanol. The ethanolic solution was filtered, made alkaline with ethanolic potassium hydroxide solution, and again filtered, and the filtrate was evaporated to dryness. The residue was extracted with light petroleum (b. p. 60—80°), the petroleum solution was filtered and the filtrate evaporated to dryness. The residue was crystallised from ethanol (charcoal), giving *2 : 6-diphenyl-4-styrylpyrimidine* (0·5 g.) in needles, m. p. 130° (Found : C, 86·2; H, 5·55; N, 8·4. $C_{24}H_{18}N_2$ requires C, 86·2; H, 5·4; N, 8·4%).

THE UNIVERSITY, NOTTINGHAM. [*Received, October 27th*, 1950.]

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75. *Reactions of the Cobaltic Ion. Part I. The Reaction of the Cobaltic Ion with Water.*

By C. E. H. BAWN and A. G. WHITE.

Aqueous solutions containing the cobaltic ion rapidly decompose, the cobalt reverting to the cobaltous state and oxygen being evolved. Results of some kinetic studies on this reaction are presented. The rate of the reaction depends in a complex manner on the hydrogen-ion concentration and its dependence on the cobaltic-ion concentration may be described by a rate equation of the form

$$-d[Co^{+++}]/dt = A[Co^{+++}] + B[Co^{+++}]^3$$

in which A and B are constants whose values depend on the temperature, ionic strength, and hydrogen-ion concentration.

It is concluded that the rate-determining step is an electron transfer between cobaltic and hydroxyl ions producing the free hydroxyl radical, but that the simplicity of this process is obscured by hydrolysis of, and complex formation involving, the cobaltic ion.

THE cobaltic ion, Co^{+++}, is stable only in the form of complex salts of which a large number are known; the only simple cobaltic salts which have so far been isolated are the fluoride, chloride, sulphate, and acetate which are all solids. On storage these salts all revert gradually to the cobaltous state.

The sulphate, which is the most readily available of the cobaltic salts, was first obtained by Marshall (*J.*, 1891, **59**, 760) by the anodic oxidation of the cobaltous salt in aqueous sulphuric acid solution. This method was further investigated by Oberer (Dissertation, " Beitrage zur Kenntniss der Kobaltisulphate," Basle, 1903) and by Swann and Xanthalsos (*J. Amer. Chem. Soc.*, 1931, **53**, 400); the latter authors devising a convenient method for its preparation.

Cobaltic sulphate is extremely reactive and will oxidise a wide variety of organic and inorganic compounds. The reaction with water follows the overall course given by the equation :

$$2Co_2(SO_4)_3 + 2H_2O = 4CoSO_4 + 2H_2SO_4 + O_2$$

and is almost instantaneous with pure water at room temperature but is markedly retarded by hydrogen ions. The first kinetic studies of the reaction were those of Oberer (*loc. cit.*) who

stated that the reaction was of first order with respect to the cobaltic-ion concentration. He proposed the following mechanism:

$$(1)\quad Co^{+++} + OH^- \longrightarrow Co^{++} + OH\cdot$$
$$(2)\quad 2OH\cdot \longrightarrow H_2O_2$$
$$(3)\quad H_2O_2 \longrightarrow H_2O + O_2$$

or

$$(4)\quad 2OH\cdot \longrightarrow H_2O + O_2$$

reaction (1) being assumed to be the slow rate-controlling step.

The work of Noyes and Deahl (*J. Amer. Chem. Soc.*, 1937, **59**, 1337) on electrolytically prepared solutions of cobaltic nitrate failed to substantiate these findings. These authors state that in the presence of 1—4N-nitric acid the reaction was kinetically complex, being of approximately second order with respect to the cobaltic ion at the start and nearly first order at the end of the reaction. They suggested that there were two simultaneous reactions, one of first and the other of second order with respect to the cobaltic-ion concentration, but were unable to offer any reaction scheme from which the observed kinetics could be derived except to suggest the occurrence of the " percobaltic," Co^{++++}, ion. However, in view of the instability of the trebly-charged ion and the large energy change to be expected for the removal of the fourth electron, this latter event appears to be extremely unlikely. In Noyes and Deahl's experiments the reactions were followed by changes in the cobaltous–cobaltic electrode potential. In all but one of their experiments silver nitrate was added as a potential mediator and was found to increase markedly the velocity of the reaction. For this reason the value of their work must be very limited.

The discrepancy between Oberer's results and those of Noyes and Deahl led to a re-examination of those of Oberer. This revealed that his results were also of a complex nature, the kinetic order with respect to the cobaltic ion varying from first to fifth according to the experimental conditions. As the principal reaction appeared to be (*a*) a simple electron-transfer reaction between ions with a rate slow enough to measure, and (*b*) a suitable method of generating free hydroxyl radicals • unaccompanied by any other products, a detailed investigation of the kinetics were carried out. Two methods were used to follow the course of the reaction. In the first the concentration of the cobaltic ion was determined directly by a volumetric method based on the reaction with ferrous salts, whilst in the second method the rate of evolution of oxygen was measured.

In view of the well-known propensity of the cobaltic ion for complex formation it was decided to check that the measurements on cobaltic sulphate solutions were not those of the rate of decomposition of some specific complex ion. To this end measurements were also carried out on solutions of cobaltic perchlorate.

Experimental.

Materials.—All reagents used were of " AnalaR " grade and no further purification was attempted.

Cobaltic Salts.—Cobaltic sulphate was prepared by Swann and Xanthakos's electrolytic method (*loc. cit.*), the solid being filtered off from the anode liquor on a coarse sintered-glass funnel, sucked free from mother liquor, dried on a porous plate, transferred to a dry bottle, and stored in a desiccator in the dark. Material prepared and stored in this manner was found to be stable for several weeks.

Attempts to obtain the perchlorate by electrolytic oxidation of cobaltous perchlorate in perchloric acid solutions were unsuccessful. Solutions of cobaltic perchlorate were therefore prepared from solutions of the sulphate in perchloric acid by double decomposition with barium perchlorate.

pH Determinations.—The pH of the reaction mixtures containing cobaltic sulphate in sulphuric acid–sodium sulphate solutions were determined by using the glass electrode and a Cambridge pH meter. The pH of the perchlorate solutions was calculated from the known quantity of perchloric acid added to the reaction mixture.

Determination of Cobaltic-ion Concentration.—Cobaltic-ion concentrations were determined by the volumetric method used by Noyes and Deahl (*loc. cit.*). In this the cobaltic salt solution was added to an excess of well-acidified ferrous ammonium sulphate, whereupon the reaction

$$Fe^{++} + Co^{+++} \longrightarrow Fe^{+++} + Co^{++}$$

occurred instantaneously. The excess of ferrous ion was then determined by back titration with standard permanganate solution. Owing to the pink colour of the cobaltous ion a potentiometric method of detecting the end point was necessary; for this purpose Garman and Droz's titrimeter (*Ind. Eng. Chem. Anal.*, 1939, **11**, 398) was used.

Kinetic Measurements.—As the reaction was one involving ions it was necessary that it should be carried out at constant ionic strength. To avoid changes in ionic strength due to conversion of cobaltic

• The decomposition of water by the cobaltic ion readily initiates vinyl polymerisation and this may be ascribed to the formation of hydroxyl radicals.

into cobaltous ion during the reaction it was therefore necessary that the total ionic strength should be large in comparison with that due to the cobalt salt alone. Further, as hydrogen ion is generated during the reaction and as this ion has a retarding effect on the rate, it was also essential that the initial total acid concentration should be large compared with that produced by the reaction.

To fulfil these requirements measurements were made on solutions which were not greater than 10^{-2}M. with respect to the cobaltic ion, had an ionic strength not less than 0·3, and a pH in the region 0—1·2. In order to vary the hydrogen-ion concentration at constant ionic strengths, use was made of sulphuric acid–sodium sulphate in the experiments on the sulphate and perchloric acid–sodium perchlorate in the experiments on the perchlorate.

Kinetic measurements were made in the usual manner by removing aliquots from the reaction mixture at suitable intervals and determining the cobaltic-ion concentration by the volumetric method described above. The reaction vessel was immersed in a thermostat the temperature of which was maintained constant to within $\pm 0{\cdot}05°$. In the case of the runs at 0° however the reaction vessel was immersed in melting ice in a large Dewar vessel. In these cases the temperature was constant over the longer periods involved only to about $\pm 0{\cdot}2°$.

In the second method of determining the rate of the reaction, its progress was followed by measurement of the amount of oxygen evolved as a function of time. The reaction vessel was immersed in a large thermostat and vigorously agitated by means of an electrically driven shaking mechanism. The amount of oxygen evolved was determined by measuring the increase of pressure in the system by means of a manometer attached directly to it by pressure tubing. The manometer was 50 cm. long and used water as manometric fluid, the scale was graduated in mm. and readings could normally be made to at least 1 mm. in each limb. The capacity of the reaction vessel was approximately 80 ml.; a baffle sealed to the reaction vessel prevented the contents from being forced up into the manometer connection by the vigorous agitation employed. A 1·5-l. vessel, immersed in a thermostat, served effectively as a constant-pressure source for the second limb of the manometer and obviated any effects of change in barometric pressure during a run.

The apparatus was calibrated, to enable pressure readings to be converted into ml. of oxygen, by connecting it through a tap to a gas burette, forcing in known volumes of gas, and noting the pressure difference produced on the manometer.

In a run, 40 ml. of the appropriate sodium sulphate–sulphuric acid–water mixture were placed in the reaction vessel and allowed to reach a steady temperature in the thermostat. At the same time 3—5 ml. of 2N-sulphuric acid, in a test-tube in the thermostat, were allowed to come to temperature equilibrium. Approximately 0·2 g. of cobaltic sulphate was weighed and added to the acid in the test-tube; the mixture was agitated until all the solid had dissolved, and 2 ml. of the solution were then added to the contents of the reaction vessel, *via* a side-arm. The stopper was immediately replaced in the side-arm, the shaker started, and the taps connecting the burette and pressure-balancing vessel to the atmosphere simultaneously closed. The moment of closure of these two taps was taken as zero time. Readings of the manometer were then made at suitable intervals.

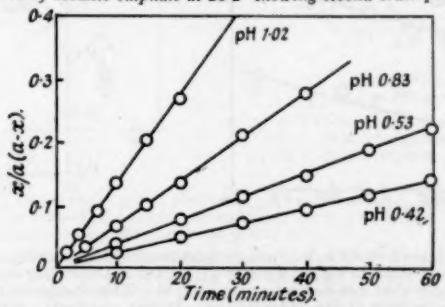
Some effect of rate of agitation of the reaction vessel on the rate of liberation of oxygen was to be expected, for except in a very slow reaction an increase in the gas–liquid interfacial area, such as is caused by shaking, must of necessity entail an increase in the rate of transfer of gas which would continue until the gas–liquid interfacial area was no longer a controlling factor in the rate of transfer of gas from one phase to the other. It was found under constant reaction conditions that the reaction velocity increased with rate of shaking and that in order to obtain results which were independent of it a shaking speed of over 350 cycles/minute was essential. All were therefore carried out at 500 cycles/minute.

Results.

Titration Method.—The results of the kinetic experiments on both sulphate and perchlorate, using the titration method and an initial cobaltic-ion concentration of $\sim 10^{-2}$N., were found in all cases to

Fig. 1.

Decomposition of cobaltic sulphate at 25·2° showing second-order plots ($\mu = 0{\cdot}32$).



agree best with a kinetic expression which was of second order with respect to the cobaltic ion. This is illustrated in Figs. 1 and 2 in which are presented two typical groups of second-order plots for a series of

runs with cobaltic sulphate at 25° and perchlorate at 20° and various pHs. In both cases it will be seen that straight lines are obtained and that the slopes, *i.e.* the second-order constants, are inversely dependent on some function of the hydrogen-ion concentration. (At lower concentrations a decrease in order was observed and this is discussed in the next section.)

It is therefore possible to write as a rate equation for the disappearance of the cobaltic ion:

$$-d[Co^{+++}]/dt = k[Co^{+++}]^2/[H^+]^x$$

Thus if the velocity constant at some fixed value of $[H^+]$ is measured the observed constant k_0 is

$$k_0 = k/[H^+]^x$$

and

$$\log_{10}k_0 = \log_{10}k + x\text{pH}$$

Therefore a plot of $\log_{10}k_0$ against pH should be linear and will permit the determination from its slope of the value of x, the order of the reaction with respect to hydrogen ion.

FIG. 2.

Decomposition of cobaltic perchlorate at 20·0°, showing second-order plots ($\mu = 1{\cdot}0$).

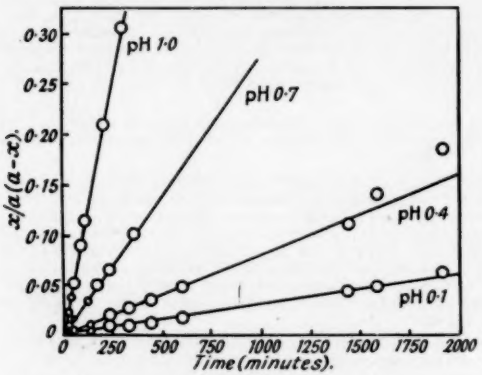


FIG. 3.

Variation of second-order velocity constant with pH. *Cobaltic sulphate* ($\mu = 0{\cdot}32$).

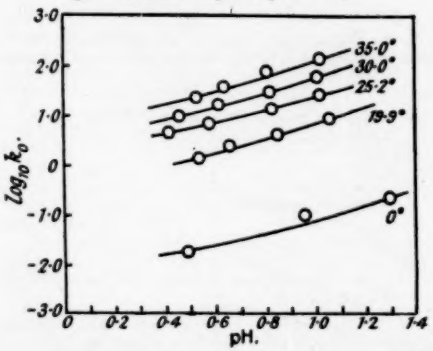


FIG. 4.

Variation of second-order velocity constant with pH. *Cobaltic perchlorate* ($\mu = 1{\cdot}0$).

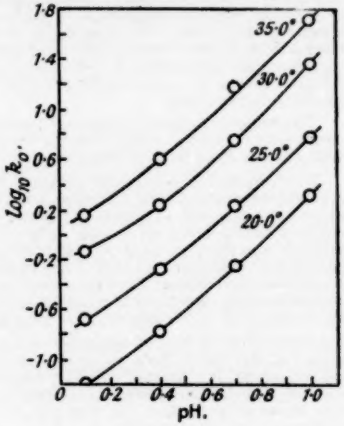
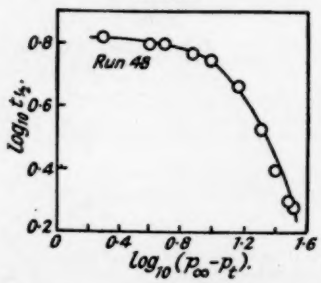


FIG. 5.

Change of order during the course of the reaction.



The results of measurements of k_0 under various conditions of temperature and pH are presented in Figs. 3 and 4 in the form of plots of $\log_{10}k_0$ against pH. It is evident that in both cases the plots are curved, and this must imply that x is dependent on the pH. This change in x with pH is interpreted (see later) in terms of hydrolysis of the cobaltic ion. Before proceeding with the analysis of these results, the corresponding results obtained from the measurement of the rate of oxygen evolution are summarised, since these bring out further interesting features of the kinetics.

Manometric Method.—The manometric experiments were carried out to discover whether there was, between the disappearance of the cobaltic ion and the production of oxygen, any slow step in the reaction sequence which might be rate-controlling for the production of oxygen, and by producing different kinetics give some clue as to the nature of the processes intervening between reactants and end products. These results at an initial concentration of about 2×10^{-3}N. obeyed neither second-order nor first-order form, but were of an intermediate order; furthermore a marked change of order occurred as the

FIG. 6.

Evaluation of k_1' and k_1' from manometric results. c expressed as $(p_\infty - p_t)$.

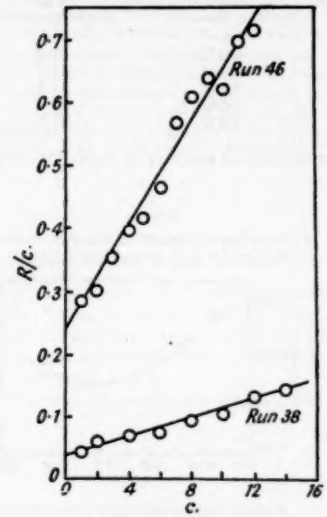


FIG. 7.

Variation of first-order velocity constant with pH. *Cobaltic sulphate : manometric experiments* (μ = 0·52).

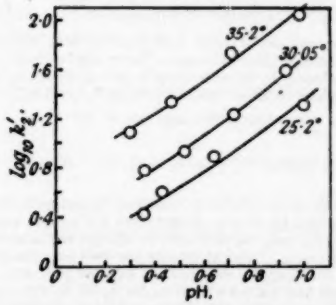


FIG. 8.

Variation of second-order velocity constant with pH. *Cobaltic sulphate : manometric experiments* (μ = 0·52)

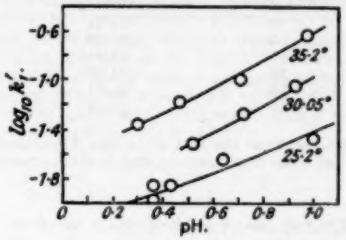
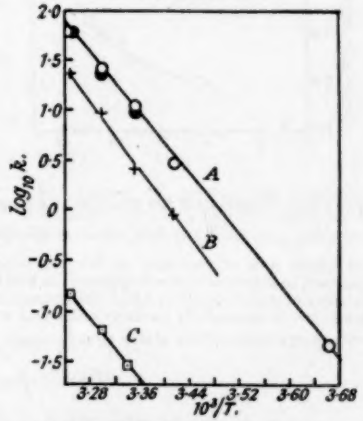


FIG. 9.

Effect of temperature.



○ *Titration experiments.*
□ *and* ● *Manometric experiments.*

A. Cobaltic sulphate, k_1', E = 35·1 kcals.
B. Cobaltic perchlorate, k_1', E = 39·6 kcals.
C. Cobaltic sulphate, k_1', E = 33·6 kcals.

reaction proceeded. Fig. 5 shows a typical plot of $\log_{10} t_{\frac{1}{4}}$ against $\log(p_\infty - p_t)$, and in all cases studied the plots were found to be curved, the slope decreasing as the concentration decreased apparently to a limiting value of zero at very low concentration (about 10^{-4}N.).

This behaviour is in agreement with that found by Noyes and Deahl (*loc. cit.*) and suggests that there must be two simultaneous reactions occurring, one of second order with respect to the cobaltic ion and the other of first order, the latter occurring at low ion concentrations.

Experiments carried out at low cobaltic-ion concentrations using the titration method confirmed the above viewpoint. As shown in the following table, the results could not be accurately represented

by a second-order equation as found at higher concentration, the order now being intermediate between first and second order. The titration method was unsuitable for exploration down to the very low concentration where the reaction becomes essentially of first order.

In view of the agreement of the results of the oxygen evolution with the behaviour found by Noyes and Deahl and of the change of order observed in the titration measurements at low concentrations, it

Temp. 25·2° c. $\mu = 0{\cdot}38$. pH = 1·1.

10-ml. samples of reaction mixture were added to 20 ml. of 0·926 N/100-$Fe(NH_4)_2(SO_4)_2$ and back titrated with $KMnO_4$ (20 ml. of $Fe(NH_4)_2(SO_4)_2$ = 35·82 ml. of $KMnO_4$). Initial $[Co^{+++}]$ = N/200.

Time (min.).	Titn. (ml. of $KMnO_4$).	$[Co^{+++}]$ as ml. of $KMnO_4$.	$k_{unl.}$ (min.$^{-1}$).	$k_{bi.}$ min.$^{-1}$ g.-ion^{-1} l.
0	22·51	13·31	—	—
5	30·20	5·62	0·172	39·9
10	32·71	3·11	0·145	47·7
20	34·22	1·60	0·106	53·2
30	34·81	1·01	0·086	59·0
40	35·08	0·74	0·072	61·8

is evident that the rate of oxygen formation is a measure of the rate of reaction of the Co^{+++} ion and not of some intermediate step in the formation of oxygen.

FIG. 10.

Effect of ionic strength on the order of the reaction with respect to cobaltic ion. Oberer's data.

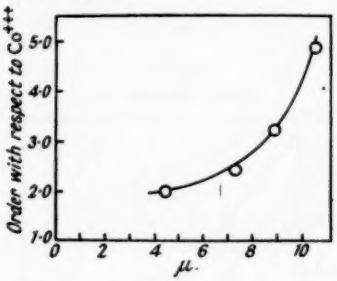
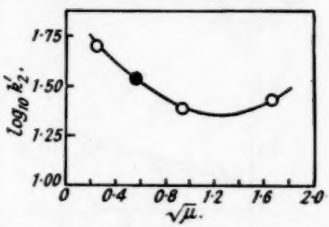


FIG. 11.

Effect of ionic strength on the second-order velocity constant for cobaltic sulphate.



○ *Values from manometric experiments.*
● *Value from titration experiments by extrapolation.*

The rate equation for the reaction at a constant pH may be written:

$$+d[O_2]/dt = -d[Co^{+++}]/dt = k_1'[Co^{+++}] + k_2'[Co^{+++}]^2$$

from which it is evident that at low concentrations the second-order term will become less and less important and the reaction will appear to be first order, whilst at high concentrations the reverse will be true. The concentration region in which the change over from first-order to second-order kinetics occurs will be marked by an apparently variable order and will depend on the relative magnitudes of k_1' and k_2'.

The correctness of the above equation may be shown by rearranging the expression, *viz.*:

$$\frac{-d[Co^{+++}]}{dt} \Big/ [Co^{+++}] = k_1' + k_2'[Co^{+++}]$$

and plotting the fraction R/c, where R is the instantaneous rate of the reaction (obtained by measurement of the slope of the c–t curve at a series of points), against the cobaltic-ion concentration (c), which would give a straight line of slope k_2' and intercept k_1'. This process was carried out on all the manometric runs and in each case R/c against c plots were found to be linear. Typical results for two experiments are shown in Fig. 6. Figs. 7 and 8 show the plot of $\log_{10}k_1'$ and $\log_{10}k_2'$ so obtained against pH, and, as previously, a set of curves was obtained. It will be seen that the values obtained for k_2 by this process agree reasonably well (taking into account the different ionic strength) with those obtained directly by the titration method.

Effect of Temperature.—The values of $\log_{10}k$ at a constant pH were read off from the $\log_{10}k$–pH curves, and the activation energy for the overall reaction derived from the $\log_{10}k - 1/T$ plot. The data are represented in Fig. 9 and correspond to the rate laws (at pH = 0·8): $k_1 = 10^{22\cdot9}e^{-35,600/kT}$ (min.$^{-1}$), $k_2 = 10^{26\cdot5}e^{-35,100/kT}$ (min.$^{-1}$ g.-mol.$^{-1}$ l.) for the sulphate; and $k_2 = 10^{29\cdot3}e^{-39,600/kT}$ (min.$^{-1}$ g.-mol.$^{-1}$ l.) for the perchlorate. As will be shown later the measured constants are composite terms, and the above relationships merely summarise the effect of temperature on the overall reaction under certain fixed conditions.

Effect of Ionic Strength.—In this connection some of the results previously given by Oberer are of interest. Oberer carried out a number of experiments at the same temperature but at widely differing ionic strengths; using his experimental data large-scale plots of concentration against time were prepared and the time of 0·9 decomposition was determined at a series of concentrations for each run. It was necessary to use the time of 0·9 decomposition in place of the more usual time of 0·5 decomposition owing to the very small concentration region over which his experiments extended. The plots of $\log_{10}t_{0\cdot9}/\log_{10}c$, for the high cobaltic-ion concentrations ($\sim 10^{-4}$N.) and small concentration range covered by each run, were linear. From the slopes of these plots the order of the reaction with respect to the cobaltic ion was determined in each case. The approximate ionic strengths of the reaction mixtures were also calculated and the values of the order of the reaction were then plotted against μ (Fig. 10). From this it is evident that the order of the reaction with respect to the cobaltic ion increases from a limiting value of 2 at low ionic strengths up to as much as 5 at very high ionic strengths. This fact must obviously be taken into account in any attempt to formulate the mechanism of the reaction.

In the present investigation of the effect of ionic strength on the velocity constant several runs were carried out by the titration method at constant pH. The values obtained for the second-order constant in these experiments are plotted as $\log_{10}k_2$ against $\sqrt{\mu}$ in Fig. 11. Also included is a point obtained by extrapolation to pH 1·15 of the $\log_{10}k_2$ — pH curve obtained from the manometric results at 25·2°. The values all fall on a smooth curve the gradient of which at low values of $\sqrt{\mu}$ is negative which is to be expected, from the Brönsted relationship, for a reaction between oppositely-charged ions.

Discussion.

The most important points which have emerged from the experimental work, and which must be explained, are :

(*a*) The $\log_{10}k$ — pH plots are curved.

(*b*) The order of the reaction with respect to the cobaltic-ion concentration is two at high concentrations and tends to unity at low concentrations.

(*c*) The order with respect to cobaltic ion also depends on the ionic strength and increases as μ is increased.

Oberer's suggestion for the mechanism of the reaction

$$\begin{aligned} Co^{+++} + OH^- &\longrightarrow Co^{++} + OH\cdot \quad (k_1)\\ 2OH\cdot &\longrightarrow H_2O_2\\ H_2O_2 &\longrightarrow H_2O + O_2 \end{aligned}$$

gives as a rate equation for the loss of the cobaltic ion :

$$-d[Co^{+++}]/dt = k_1[Co^{+++}][OH^-]$$

or, in terms of $[H^+]$: $-d[Co^{+++}]/dt = k_1K_w[Co^{+++}]/[H^+]$, where K_w is the ionic product of water, and is clearly inadequate. If it is assumed that in addition to the above reactions the cobaltic ion is capable of being hydrolysed in aqueous solutions then the following additional processes occur :

$$Co^{+++} + H_2O \rightleftharpoons CoOH^{++} + H^+ \quad (K_1)$$

(This should be more correctly written as

$$Co(H_2O)_6^{+++} \rightleftharpoons \{Co(H_2O)_5(OH)\}^{++} + H^+$$

but the above form is retained for convenience of representation.)

$$CoOH^{++} + OH^- \longrightarrow CoOH^+ + OH\cdot \quad (k_2)$$

This scheme yields as a rate equation for the loss of the cobaltic ion :

$$-d[Co^{+++}]_T/dt = k_1[Co^{+++}][OH^-] + k_2[CoOH^{++}][OH^-] \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$= [Co^{+++}]\left\{\frac{k_1K_w}{[H^+]} + \frac{k_2K_1K_w}{[H^+]^2}\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$= \frac{[Co^{+++}]_T}{\left\{1 + \frac{K_1}{[H^+]}\right\}}\left[\frac{k_1K_w}{[H^+]} + \frac{k_2K_1K_w}{[H^+]^2}\right] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where $[Co^{+++}]_T$ is the total titratable cobaltic ion in the solution, which is assumed to be $(Co^{+++} + CoOH^{++})$. The expression (2), which is of the same form as (3), holds if only Co^{+++} is titratable. These equations are obviously much nearer the truth and are at least adequate to

explain the kinetics in very dilute solutions where the reaction is of first order with respect to the cobaltic ion. The observed velocity constant k_0 is

$$k_0 = \left[\frac{k_1K_w}{[H^+]} + \frac{k_2K_1K_w}{[H^+]^2}\right] \Big/ \left[1 + \frac{K_1}{[H^+]}\right]$$

This will give a $\log_{10}k_0$ — pH plot which is curved and the slope of which varies from 1 in the region where hydrolysis is negligible to 2 in the region where it is extensive. The exact region of hydrogen-ion concentration over which the change will occur will depend both on the magnitude of K_1 and on the fraction k_2/k_1.

This scheme does not account for the variable order of the reaction with respect to the cobaltic ion, and the occurrence of second-order reaction at high concentration is not allowed for. The only way of explaining these observations without involving extremely improbable termolecular steps or the production of the " percobaltic ion " suggested by Noyes and Deahl would appear to be the assumption that the cobaltic ion is capable of forming complexes in aqueous solution which contain more than one cobaltic ion. Whether these complexes can be considered to be true complex ions involving ordinary valency linkages or whether they are to be regarded as the ion-association groups first postulated by Bjerrum (*Kgl. Danske Vidensk. Selskab.*, 1926, **7**, No. 9), and involving only a loose physical association, cannot be readily decided. The occurrence of a reaction of fifth order with respect to the cobaltic ion in concentrated salt solutions (*loc. cit.*) would appear to favour the latter, a true complex ion containing five cobaltic ions being a little improbable. It is however possible that both types of linkage occur, for at any rate in the sulphate solutions a structure such as

$$(H_2O)_5Co^{++}\text{–}SO_4\text{–}Co^{++}(H_2O)_5$$

is not impossible, whilst in the perchlorate solutions a structure of the type

$$(H_2O)_5Co^{++}\text{–}O\text{–}\overset{++}{C}o(H_2O)_5$$

similar to those postulated in the case of ceric ions by Sherrill, King, and Spooner (*J. Amer. Chem. Soc.*, 1943, **65**, 170) may arise.

If the existence of dimeric complex ions is assumed and if these can react in the same way as the single cobaltic ion discussed above, then a rate equation may be derived which includes terms in the first and second powers of the cobaltic-ion concentration. Such an equation qualitatively fits all the observed facts but must at the present be regarded as speculative until more information is available regarding the existence of hydrolysis and complex-ion formation in solution. It is hoped to obtain this information by spectroscopic investigations.

Finally, the possible decomposition of the cobaltic ion by direct reaction with water rather than the hydroxyl ion requires discussion. This reaction has been suggested by Weiss (*Naturwiss.*, 1935, **23**, 64):

$$\begin{aligned} Co^{+++} + H_2O &\longrightarrow Co^{++} + H_2O^+ \\ H_2O^+ &\rightleftharpoons H^+ + OH \\ 2OH &\longrightarrow H_2O + O_2 \end{aligned}$$

This mechanism, as it stands, cannot explain our experimental findings since it would predict that the decomposition of the Co^{+++} would be independent of hydrogen-ion concentration and that only the rate of oxygen production would vary with pH. This objection would be removed if the first reaction were reversible but this would require that the cobaltous ion should also exert an inhibitory effect on the reaction, which has not been observed. We therefore conclude that the direct reaction between water and cobaltic ion plays no part in the thermal reaction.

THE UNIVERSITY, LIVERPOOL. [*Received, July 25th*, 1950.]

76. *Reactions of the Cobaltic Ion. Part II. The Kinetics of the Reaction of the Cobaltic Ion with Formic Acid.*

By C. E. H. Bawn and A. G. White.

The oxidation of formic acid by the cobaltic ion in 2—8N-sulphuric acid occurs according to the stoicheiometric equation :

$$2Co^{+++} + HCO_2H \longrightarrow CO_2 + 2Co^{++} + 2H^+$$

The rate-determining process has been shown to be the electron-transfer reactions

$$Co^{+++} + HCO_2H \longrightarrow Co^{++} + HCO_2 + H^+$$
$$Co^{+++} + HCO_2^- \longrightarrow Co^{++} + HCO_2$$

The dependence of the reaction rate on temperature and ionic strength has been measured. The reactions of the formyl radical are discussed.

The oxidation–reduction potential of the cobaltic–cobaltous system is so high (~1·8 v.) that the cobaltic ion should be capable of oxidising a wide variety of organic compounds. The only relevant experiments which have been reported are those of Swann and Xanthakos (*J. Amer. Chem. Soc.*, 1931, **53**, 400), who found that cobaltic sulphate would oxidise pentene, benzene, acetic acid, ethyl alcohol, acetone, and glycerol and would quantitatively oxidise ethylene glycol, formic acid, tartaric acid, citric acid, and malic acid to carbon dioxide. It has also been found recently (Tipper, private communication) that cobaltic sulphate in 5—10N-sulphuric acid reacts readily with acetylene, carbon dioxide being one of the products, whilst the present authors have observed that under similar conditions reaction also occurs with dioxan, sugars, alcohols, and formaldehyde. Cobaltic sulphate in acid media also initiates the polymerisation of vinyl compounds.

Some preliminary kinetic experiments on a few representative organic compounds have therefore been made in order to gain some insight into the general features of the mechanisms of these reactions. These results are reported in the following paper, and the present investigation deals with the oxidation of formic acid which has been studied in greater detail.

As the cobaltic ion decomposes in aqueous solution with the liberation of the hydroxyl radical (preceding paper) it was possible that the reactions with organic compounds would be those of that radical. This view however would appear to be untenable for the following reason. The experiments reported in this and the subsequent paper were carried out in 2·5—10N-sulphuric acid. Under these conditions, with a cobaltic-ion concentration of $\sim 10^{-2}$M., the reaction with water at room temperature is very slow and takes several days to complete, but on addition of the organic compound ($\sim 10^{-1}$M.) the reaction goes to completion in 30—60 minutes. It would therefore appear that the cobaltic ion itself must react directly with the organic compound and not merely serve as a source of hydroxyl radicals.

Experimental.

Materials.—All reagents used were of AnalaR grade. Cobaltic sulphate was prepared by Swann and Xanthakos's method (*J. Amer. Chem. Soc.*, 1931, **53**, 400).

Estimation of Cobaltic Ion.—This was carried out by Noyes and Deahl's method as described in the preceding paper.

Kinetic Measurements.—Rate of reaction of cobaltic ion. Mixtures containing the appropriate concentrations of formic acid, sulphuric acid, and potassium hydrogen sulphate, to give the hydrogen-ion concentration and ionic strength required, were allowed to reach a steady temperature in a vessel immersed in a thermostat. A roughly weighed quantity of cobaltic sulphate was then added, to give an initial cobaltic-ion concentration of ~N/100. Samples were removed at appropriate intervals and analysed for cobaltic ion. Below room temperature a large Dewar vessel containing water cooled with ice was used in place of a thermostat. All experiments were carried out in a large excess of formic acid so that its concentration could be regarded as constant.

The hydrogen-ion concentration in the sulphuric acid–potassium hydrogen sulphate used was calculated on the basis of the two following assumptions :

(*a*) The dissociation $H_2SO_4 \longrightarrow H^+ + HSO_4^-$ was complete, and

(*b*) The dissociation $HSO_4' \longrightarrow H^+ + SO_4^{--}$ could be neglected.

Rate of evolution of carbon dioxide. The apparatus consisted of a conical flask with a ground-glass stopper carrying a short length of capillary tubing. A side arm of approximately 7—8 ml. capacity fitted with small ground-glass stopper was fused on to the vessel. The whole was immersed in a thermostat and vigorously agitated by means of an electrically driven rocking mechanism. The vessel

was connected through a length of narrow-bore pressure tubing and a three-way tap to a water manometer (50 cm.). The other limb of the manometer was connected to a large vessel immersed in the thermostat and possessing a tap connecting it to the atmosphere. This vessel effectively served as a constant-pressure source and obviated any effects of changing atmospheric pressure.

The appropriate solution of formic acid, potassium hydrogen sulphate and part of the sulphuric acid was placed in the flask. In the side arm were placed 5 ml. of a solution of cobaltic sulphate in sulphuric acid sufficient to give, when mixed with the bulk of the solution a cobaltic-ion concentration of N/100 and to bring the sulphuric acid concentration to the desired value. The shaker was started immediately after the mixing, and the taps connecting the apparatus with the atmosphere were simultaneously closed. This time was taken as the zero, and the rate was followed by reading the manometer at convenient intervals.

Stoicheiometric Measurements.—The apparatus consisted of the reaction vessel used to investigate the rate of carbon dioxide production connected by pressure tubing and a three-way tap to a gas burette.

As in the kinetic experiments a solution of formic acid, potassium hydrogen sulphate and part of the sulphuric acid was placed in the flask and at the same time a test-tube containing 10—15 ml. of a sulphuric acid solution of cobaltic sulphate of the appropriate concentration was allowed to reach temperature equilibrium in the thermostat. 5 Ml. of the cobaltic solution were removed for cobaltic-ion content determination, and a further 5 ml. of the solution were placed in the side-arm of the reaction vessel, and the tap connecting the system with the atmosphere closed. The gas burette was then read, the contents of side arm and vessel mixed and reaction allowed to proceed to completion with occasional vigorous agitation.

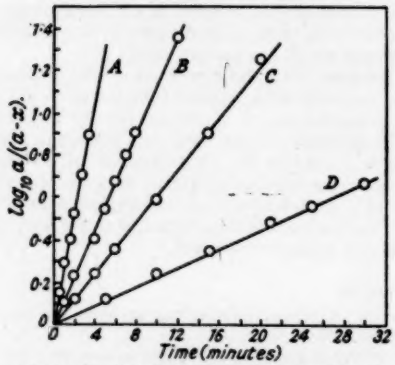
To correct for the volume of carbon dioxide dissolved by the reaction mixture a series of experiments was carried out in which the cobaltic ion in the side-arm was replaced by a standard solution of sodium hydrogen carbonate. Observed and calculated carbon dioxide evolutions were then compared, and from the results correction factors were obtained which could be applied to the stoicheiometric experiments.

Results.

Formic Acid.—In the presence of a large excess of formic acid the rate of disappearance of the cobaltic ion was found to be accurately of first order. Fig. 1 shows a typical group of first-order plots for various

Fig. 1.

Oxidation of formic acid by cobaltic ion.

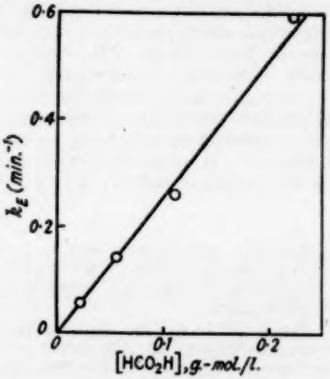


First-order plots for the rate of the reaction of cobaltic ion.

Initial $[Co^{+++}] \sim$ N/200, $T = 30{\cdot}5°$; *medium*, 5N-*sulphuric acid.* $[HCO_2H]$: *A*, 0·221; *B*, 0·111; *C*, 0·0553; *D*, 0·0221, *g.-mol./l.*

Fig. 2.

Effect of formic acid concentration on the rate of the reaction of cobaltic ion. $T = 30{\cdot}5°$; *medium*, 5N-*sulphuric acid.*



formic acid concentrations. The values of the first-order constants thus obtained were also found to be a linear function of the formic acid concentration, as is shown in Fig. 2. The rate equation is thus

$$-d[Co^{+++}]/dt = k[HCO_2H][Co^{+++}]$$

However, it is also possible that in addition to the undissociated formic acid molecule the formate ion may react with the cobaltic ion, the rate equation in this case being

$$-d[Co^{+++}]/dt = k_1[HCO_2H][Co^{+++}] + k_2[HCO_2^-][Co^{+++}]$$

As in the above measurements the formic acid was in large excess, its concentration can be regarded as constant. The hydrogen-ion concentration was also constant, since all the measurements were made in 5N-sulphuric acid, and thus the concentration of formate ion may be regarded as constant;

consequently the reaction would still appear accurately first order with respect to the cobaltic ion. The observed first-order constant k_0 would be given by

$$k_0 = k_1[HCO_2H] + k_2[HCO_2^-]$$

In order to confirm that the formate ion as well as the molecule was a reactive entity a series of runs was carried out at constant ionic strength and formic acid concentration but at a series of different hydrogen-ion concentrations and temperatures. Since $[HCO_2^-] = K[HCO_2H]/[H^+]$, where K is the dissociation constant of formic acid, the above rate equation may now be expressed as

$$-d[Co^{+++}]/dt = \{k_1[HCO_2H] + k_2K[HCO_2H]/[H^+]\}[Co^{+++}]$$

The apparent first-order constant k_E, obtained in the presence of a large excess of formic acid, will be given by the term in the braces and would show a linear dependence on $1/[H^+]$. The values of the first-order constant obtained at temperatures from 0° to 30° are shown plotted against $1/[H^+]$ in Fig. 3. It will be seen that in all cases a linear relationship is obtained, in complete harmony with the above view of the processes contributing to removal of cobaltic ion.

The values of the two rate constants k_1 and k_2 can readily be obtained from the intercepts and slopes, respectively, of the plots shown in Fig. 3, if the value of K under the experimental conditions is known. Direct measurement of K in the medium used (sulphuric acid–potassium hydrogen sulphate solutions)

FIG. 3.

Effect of temperature on the rate of the reaction of cobaltic ion with formic acid (μ = 4·0).

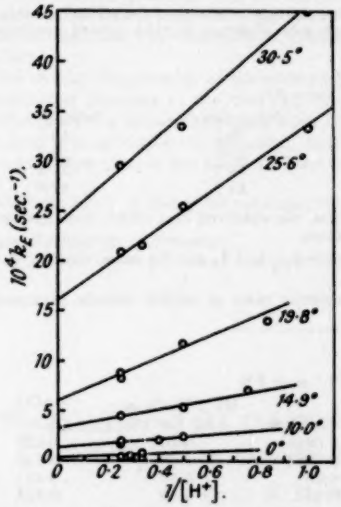
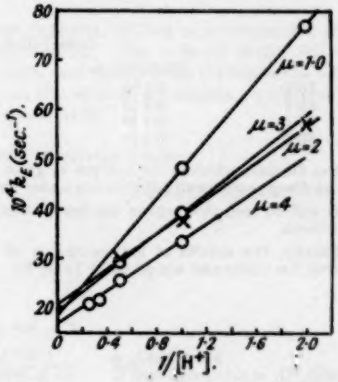


FIG. 4.

Effect of ionic strength. T = 25·6°.



is not practicable. Consequently it was necessary to use values of K reported for other media. Values of K obtained by Kiss and Virmanczy (*Z. physikal. Chem.*, 1934, *A*, **171**, 25) and Larsson and Adele (*ibid.*, 1931, *A*, **156**, 381) at ionic strengths of up to 4 in potassium chloride and sodium chloride have been utilised and values of K at temperatures other than those covered by these measurements were obtained by application of the Harned and Embree (*J. Amer. Chem. Soc.*, 1934, **56**, 1050) relationship between K and temperature.

The values of k_1 and k_2 thus obtained at different temperatures are given in Table I.

TABLE I.

k_1 and k_2 in sec.$^{-1}$ g.-mol.$^{-1}$ l.; ionic strength = 4·0.

T, ° K.	303·6	298·7	292·9	288·0	283·1	273·1
10^3k_1	29·7	13·0	4·72	2·14	0·886	0·190
k_2	440	161	99·3	56·0	25·4	6·95

The energies of activation for the two reactions were obtained from the slopes of plots of $\log_{10}k$ against $1/T$, the values obtained being :

for k_1, E_1 = 26·9 kcal./mol.; for k_2, E_2 = 21·7 kcal./mol.

The corresponding frequency factors, A_1 and A_2, calculated from the Arrhenius equation were $A_1 = 6{\cdot}76 \times 10^{17}$ and $A_2 = 1{\cdot}95 \times 10^{16}$, respectively.

The values of the entropy of activation for the reactions were then calculated by means of the statistical mechanical expression for the frequency factor of a bimolecular reaction in solution (Glasstone, Laidler, and Eyring," Theory of Rate Processes," McGraw Hill, 1941):

$$A = \frac{ekT}{h} e^{\frac{\Delta S}{R}}$$

The values obtained being : for k_1, $\Delta S_1 = 21{\cdot}1$ cal./°c; for k_2, $\Delta S_2 = 23{\cdot}2$ cal./°c.

The effect of ionic strength on the rate of the reaction is presented in the form of a plot of k_E against $1/[H^+]$ for various ionic strengths in Fig. 4. The values of k_1 and k_2 derived from these results together with the values of K used in the calculation of k_2 are given in Table II.

TABLE II.

k_1 and k_2 in sec.$^{-1}$ g.-mol.$^{-1}$ l.; $T = 25{\cdot}6°$ c.

μ.	1.	2.	3.	4.
10^3k_1	15·7	16·6	16·8	13·1
10^4K	2·92	2·05	1·33	0·846
k_2	78·5	71·6	97·1	162

These results do not obey the Brønsted relationship because of the high values of μ, although the effect of μ on k_1 is much smaller than that on k_2, as would be expected from the fact that k_1 refers to an ion–molecule and k_2 an ion–ion reaction.

Results obtained by measurement of the rate of carbon dioxide production are given in Table III. The column k_{CO_2} gives the experimentally determined first-order constant for the rate of evolution of

TABLE III.

Initial $[Co^{+++}] =$ N/200; $\mu = 4{\cdot}0$.

T, ° c.	$[HCO_2H]$, N.	$[H^+]$, N.	$10^4k_{CO_2}$ (sec.$^{-1}$).	10^4k_E (sec.$^{-1}$).
25·1	0·125	4·0	19·1	19·0
25·1	0·125	2·0	22·9	23·2
25·1	0·219	4·0	33·6	33·4
30·3	0·125	4·0	41·9	47·8

carbon dioxide, whereas the column k_E gives, for comparison, the observed first-order constants for the rate of disappearance of cobaltic ion under identical conditions.

It will be seen that within the limits of experimental error k_{CO_2} and k_E are the same, under identical conditions.

Finally, the results of measurements of the stoicheiometric ratio of carbon dioxide produced to cobaltic ion consumed are given in Table IV.

TABLE IV.

$T = 29°$ c.; $[H^+] = 4$N.; $\mu = 2{\cdot}0$.

$[HCO_2H]$, N.	Ml. $KMnO_4$ ≡ 5 ml. Co^{+++}.	$\frac{+\Delta CO_2}{-\Delta Co^{+++}}$.	$[HCO_2H]$, N.	Ml. $KMnO_4$ ≡ 5 ml. Co^{+++}.	$\frac{+\Delta CO_2}{-\Delta Co^{+++}}$.
0·0625	5·18	0·521	0·0625	6·10	0·525
0·0625	4·66	0·502	0·0625	7·08	0·516
0·0625	4·99	0·496	0·25	6·88	0·511
0·0625	4·96	0·488	0·25	9·16	0·525
0·0625	4·72	0·522			

Variation of either $[HCO_2H]$ or $[Co^{+++}]$ does not affect this ratio, the value of which may be taken to be 0·5 within the limits of experimental error.

DISCUSSION.

The oxidation of formic acid by cobaltic ion was shown by Swan and Xanthakos to lead to a 100% yield of carbon dioxide. Thus any postulated reaction mechanism should not only account for this product but also yield correct kinetics and explain the stoicheiometric relationships observed. The following sequence of reactions satisfactorily accounts for these facts.

$$HCO_2H + Co^{+++} \longrightarrow HCO_2\cdot + H^+ + Co^{++} \quad (1)$$

$$HCO_2^- + Co^{+++} \longrightarrow HCO_2\cdot + Co^{++} \quad (2)$$

$$HCO_2H \rightleftharpoons HCO_2^- + H^+ \quad (3)$$

$$HCO_2\cdot + H_2O \rightleftharpoons HCO_2H + OH\cdot \quad (4) \text{ and } (5)$$

$$OH\cdot + HCO_2\cdot \longrightarrow CO_2 + H_2O \quad (6)$$

$$HCO_2\cdot + HCO_2\cdot \longrightarrow HCO_2H + CO_2 \quad (7)$$

$$HCO_2\cdot + Co^{+++} \longrightarrow Co^{++} + H^+ + CO_2 \quad (8)$$

Primary electron-transfer processes of the type (1) and (2) are necessary to explain the observed kinetics and are also in harmony with investigations on the reactions of cobaltic ions with water and other organic molecules. The exact fate of the formyl radical thus formed is, however, much less certain. The possible secondary-reaction schemes (4), (5), and (6), or (7), conform to the experimental findings, each leading to the experimental stoicheiometric fraction for CO_2/Co^{+++} of 0·5 and also to the observed rate equation. The occurrence of reaction (5) has already been postulated by Weiss (*J. Phys. Chem.*, 1937, **41**, 1107) to explain the oxidation of formic acid by hydrogen peroxide. Although reaction (4) may require a small activation energy it should occur readily at room temperature. Reactions (6) and (7), involving the transfer of a hydrogen atom between a pair of radicals, would be equally probable and require little or no activation.

An unequivocal decision between these alternative secondary reactions is thus not possible but the former is more likely since, owing to the overwhelming concentration effect of the water, the formyl radical would be preferentially consumed by reaction (4) rather than (7).

Reaction (8) which is also a possible source of carbon dioxide may be excluded since its occurrence would lead to a kinetic dependence of the cobaltic-ion concentration different from that observed.

It is not our intention to discuss the theoretical aspects of the elementary processes in this paper but it is noteworthy that the activation energy of the reaction of the cobaltic ion with the formate ion is 5·2 kcal. less than with the formic acid molecule. This is understandable as in the former case the electrostatic energy of interaction is available to bring the reactants together.

The similar magnitudes of the entropies of activation indicate, as was to be expected, that the activated complex in the two cases must be closely similar. The entropy factor for the ion–ion reaction is larger than for the ion–molecule reaction, and this is understandable as there must be a greater change in solvation on the formation of the activated complex, of charge 2^+, in the first case than in the second where the charge remains at 3^+.

We thank Mr. J. A. Sharp for assistance with the experimental measurements.

THE UNIVERSITY, LIVERPOOL. [*Received, July 25th*, 1950.]

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77. *Reactions of the Cobaltic Ion. Part III. The Kinetics of the Reactions of the Cobaltic Ion with Aldehydes and Alcohols.*

By C. E. H. BAWN and A. G. WHITE.

The preliminary results of a study of the reactions of the cobaltic ion with formaldehyde and methyl, ethyl, and *n*-propyl alcohols in aqueous 5N- and 10N-sulphuric acid are summarised. The rate equations have been determined in each case, and various mechanisms for the reactions are discussed. In general the results would appear to be consistent with the assumption that the first step is an electron-transfer reaction between the cobaltic ion and the organic compound with the generation of a free radical. The secondary reactions of the various types of free radicals thus formed are discussed.

IN the preceding paper the powerful oxidising action of the cobaltic ion towards a wide variety of organic compounds was summarised, and in particular a detailed kinetic study of the oxidation of formic acid was reported. In the present paper this work has been extended to other simple organic molecules, and the preliminary results of the reactions of the cobaltic ion with formaldehyde and the simple alcohols are summarised. Although it has not yet been possible to determine the reaction mechanism with the degree of completeness achieved with formic acid the results are consistent with the view that the primary reaction is an electron-

transfer reaction between the cobaltic ion and the organic molecule with the formation of a formyl or alkoxyl radical.

Experimental.

Materials.—All reagents used, with the exception of cobaltic sulphate, were of "AnalaR" grade, and no further purification was attempted. The cobaltic sulphate was prepared as described in the preceding paper.

Kinetic Measurements.—These were carried out in 5N- or 10N-sulphuric acid to suppress the reaction of the cobaltic ion with water and permit a study of the reaction with the organic compound alone. The runs were always carried out in the presence of a considerable excess of the organic compound so that its concentration could be regarded as constant, and were followed by determination of the cobaltic-ion concentration in the reaction mixture by the titration methods described in Parts I and II (*J.*, 1951, 331, 339). Where the reaction proceeded too rapidly for the normal method of sampling to be used the reaction was carried out in a series of tubes, being started by addition of the organic compound to a tube and stopped by addition of excess of standard ferrous ammonium sulphate after a known time interval.

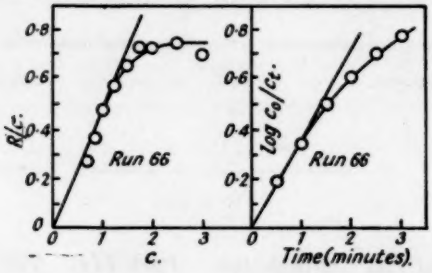
For runs above room temperature the reaction vessel was immersed in a bath with temperature thermostatically controlled to $\pm 0{\cdot}05°$, while for runs between 0° and room temperature the reaction vessel was immersed in water, cooled to the appropriate temperature with ice, in a large Dewar vessel. By this latter means the temperature of the reaction mixture could be held constant, over the relatively short period required for a run, to within $\pm 0{\cdot}1°$.

Results.

Formaldehyde.—In the presence of a large excess of this compound the rate of disappearance of the cobaltic ion was neither of first- nor second-order form ([Co^{+++}] approximately $0{\cdot}5 \times 10^{-4}$M.), and in order

Fig. 1.

Reaction of the cobaltic ion and formaldehyde. Typical R/c against c and first-order plots.



to determine the form of the overall rate equation the following method was used. Plots were prepared of the cobaltic-ion concentration (c) against time (t), and tangents drawn to these at selected values of c. The slope of the tangents thus gave the instantaneous rate of reaction (R) at that concentration. Finally R/c was plotted against concentration. It was found, as is shown by a typical plot in Fig. 1, that the reaction was of a variable order with respect to cobaltic-ion concentration, the overall rate being approximately of second order at low concentrations (*i.e.*, R/c proportional to concentration) and approximately of first order at high concentrations (*i.e.*, R/c independent of concentration). These facts may be satisfactorily accounted for by a rate equation * of the form

$$-d[Co^{+++}]/dt = k_1[Co^{+++}]^2/(A + k_2[Co^{+++}])$$

for if at low concentration $A \gg k_2[Co^{+++}]$ it reduces to

$$-d[Co^{+++}]/dt = k_1[Co^{+++}]^2/A$$

while at high concentrations if $k_2[Co^{+++}] \gg A$ it reduces to

$$-d[Co^{+++}]/dt = k_1[Co^{+++}]/k_2$$

the order at intermediate concentrations being variable as was found experimentally. The values of k_1/k_2 and k_1/A were derived from the initial slopes of first order (*i.e.*, $\log_{10} c/t$) and R/c versus c plots, respectively. The initial portions of the first-order plots (*i.e.*, the high-concentration region) were

* An equation of the form $-d[Co^{+++}]/dt = k_1'[Co^{+++}] + k_2'[Co^{+++}]^2$ cannot account for the form of the $\frac{d[Co^{+++}]}{dt} \Big/ [Co^{+++}]$ against $[Co^{+++}]$ plot (Fig. 1).

all found to be linear but the initial portions of R/c against c plots had in most cases to be obtained by extrapolation.

To determine the manner in which the formaldehyde concentration affected the rate, values of k_1/A and k_1/k_2 obtained at 0° for various formaldehyde concentrations were plotted against various functions of this concentration. It was found that both k_1/A and k_1/k_2 were proportional to the formaldehyde concentration, but the latter plot did not pass through the origin (Figs. 2*A* and 2*B*).

The results of experiments at constant formaldehyde concentration and different temperatures are presented in Fig. 3. In the limited temperature range over which it was possible to work (0—10°), the

FIG. 2*A*.

Reaction of cobaltic ion with formaldehyde in 5N-sulphuric acid at 0°.

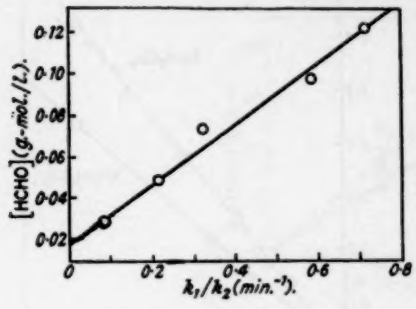
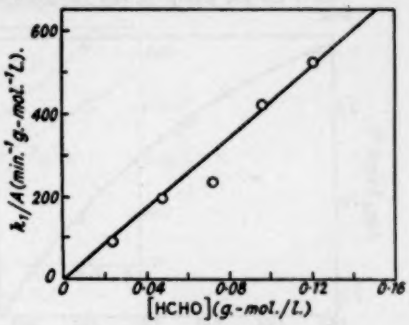


FIG. 2*B*.



k_1/A plot was linear while that for k_1/k_2 was curved. The linearity of the k_1/A plot must imply either that A is temperature independent or that k_1 and A have approximately the same temperature coefficient.

Since formaldehyde reacts very rapidly with the cobaltic ion and its oxidation product formic acid reacts some 100 or more times more slowly it is very likely that in the presence of excess of formaldehyde the main product of oxidation is formic acid.

FIG. 3.

Effect of temperature on the reaction between cobaltic ion and formaldehyde in 5N-sulphuric acid.

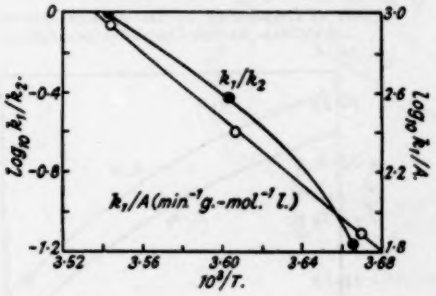
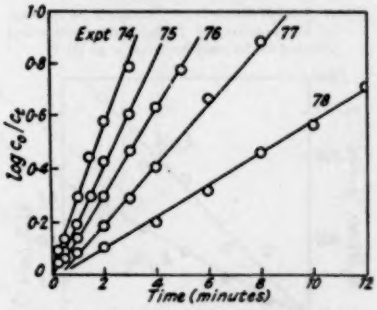


FIG. 4.

Reaction of cobaltic ion with methyl alcohol, showing first-order rate law.



Primary Aliphatic Alcohols.—The reactions of methyl, ethyl, and *n*-propyl alcohol with the cobaltic ion have been examined. The oxidation of methyl alcohol appears to be more complex than those of the other two compounds, which gave similar results and thus are oxidised according to a common mechanism.

Methyl alcohol. The reaction showed a well-defined short induction period which increased with decrease in concentration of methyl alcohol. With considerable excess of methyl alcohol in 5N-sulphuric acid and initial cobaltic-ion concentrations of about $0{\cdot}5 \times 10^{-4}$M. the rate of disappearance of cobaltic ion obeyed a first-order law. These facts are clearly shown in Fig. 4 which gives the first-order plots for the disappearance of cobaltic ion at various methyl alcohol concentrations. This first-order constant

was directly proportional to the methyl alcohol concentration. Hence the rate of the reaction after the induction period may be represented by

$$-d[Co^{+++}]/dt = k[Co^{+++}][MeOH]$$

The results of the temperature dependence of the reaction velocity are shown in Fig. 5. It is at once evident from the non-linearity of the plot that k must be a complex quantity containing more than one factor which is temperature dependent.

FIG. 5.

Effect of temperature on the reaction between cobaltic ion and methyl alcohol 5N-sulphuric acid.

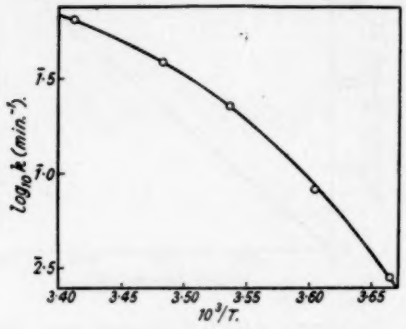
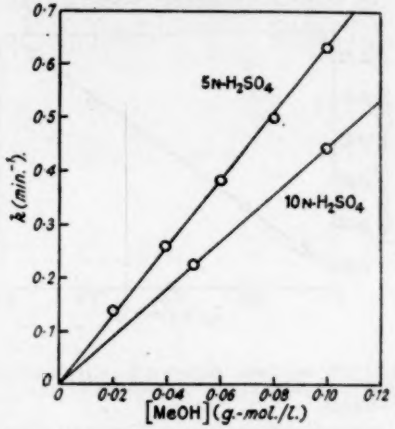


FIG. 6.

Effect of methyl alcohol concentration on the rate of the reaction of cobaltic ion with methyl alcohol in 5N- and 10N-sulphuric acid at 20·1°.



The results of two experiments at different methyl alcohol concentrations in 10N-sulphuric acid, and the first-order constants so obtained, are included in Fig. 6. It will be seen that an increase in the acid concentration causes a marked decrease in the rate of the reaction.

No gas formation was observed during the reaction, and the product was shown to be largely if not entirely formic acid. Separation of the formic acid by distillation and determination by titration showed

FIG. 7.

Effect of ethyl alcohol concentration on the rate of the reaction of cobaltic ion with ethyl alcohol in 5N-sulphuric acid at 20·1°.

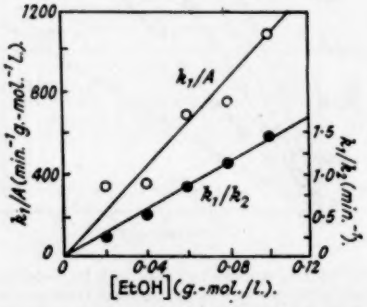
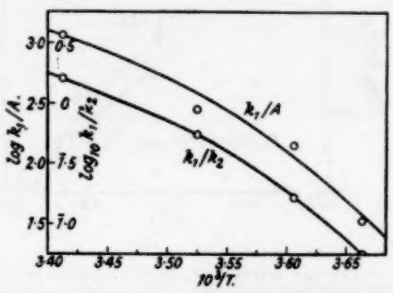


FIG. 8.

Effect of temperature on the reaction between cobaltic ions and ethyl alcohol in 5N-sulphuric acid.



that over a five-fold range of alcohol concentration the fraction—moles of acid produced/cobaltic ion consumed—was equal to 1·0, within the experimental error.

Ethyl alcohol. The rate of disappearance of the cobaltic ion in the presence of a large excess of ethyl alcohol in 5N-sulphuric acid was found to be best fitted by a rate equation of the same form as that required for formaldehyde, *viz.*

$$-d[Co^{+++}]/dt = k_1[Co^{+++}]^2/(A + k_2[Co^{+++}])$$

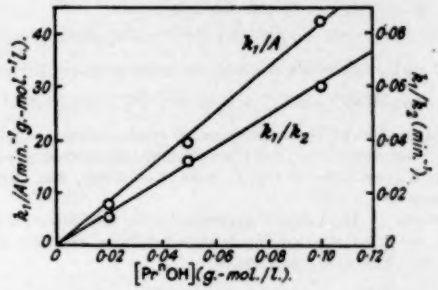
As with formaldehyde, values of k_1/A were obtained from the initial slopes of plots of R/c against c and values of k_1/k_2 were obtained from the initial slopes of first-order plots. The data thus obtained being used, the plots of k_1/A and k_1/k_2 were found to be directly proportional to the ethyl alcohol concentration as is shown in Fig. 7. Thus the rate equation for the loss of cobaltic ion may be expressed as

$$-d[Co^{+++}]/dt = k_1[EtOH][Co^{+++}]^2/(A + k_2[Co^{+++}])$$

Runs were carried out at a number of temperatures to examine the temperature dependence of k_1/A and k_1/k_2, and the results obtained are shown in Fig. 8. Curves were obtained in both cases indicating, as was to be expected, different temperature coefficients for each of the constants A, k_1, and k_2.

FIG. 9.

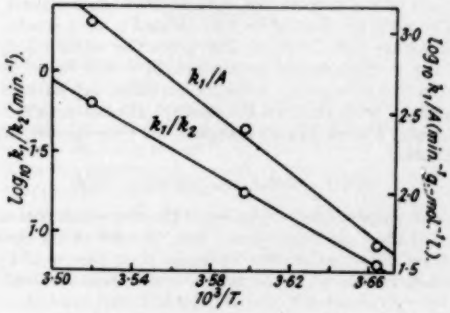
Effect of n*-propyl alcohol concentration on the rate of the reaction between the cobaltic ion and* n*-propyl alcohol in* 5N*-sulphuric acid at* 0°.



n*-Propyl alcohol.* The results obtained with this compound were exactly parallel to those with ethyl alcohol, and obeyed the same rate equation. As before, values of k_1/A and k_1/k_2 were proportional to the *n*-propyl alcohol concentration, as is shown in Fig. 9. In this case, however, plots of $\log_{10} k_1/A$ and $\log_{10} k_1/k_2$ against $1/T$ were found to be linear (Fig. 10).

FIG. 10.

Effect of temperature on the rate of the reaction between n*-propyl alcohol and the cobaltic ion in* 5N*-sulphuric acid.*



DISCUSSION.

Mechanism of Oxidation of Formaldehyde.—The initiation step in the oxidation is the reduction of the cobaltic ion to the cobaltous state and this may be conveniently represented by

$$HCHO + Co^{+++} \longrightarrow CHO\cdot + H^+ + Co^{++}$$

It is highly probable that the cobaltic ion is co-ordinated to water, and the preliminary process leading to decomposition or reaction may be the replacement of one of the co-ordinated molecules of the cobaltic shell by formaldehyde. Although there is no direct evidence for this replacement in this particular case aldehydes are known to form complexes with other heavy-ion salts (Davis and Green, *J. Amer. Chem. Soc.*, 1940, **62**, 1272). Initial complex formation therefore

being assumed, the following reaction mechanism is proposed which is in broad agreement with the experimental findings:

$$\begin{aligned}
HCHO + Co^{+++} &\longrightarrow (HCHO{\cdot}Co^{+++}) && (1)\\
(HCHO{\cdot}Co^{+++}) &\longrightarrow Co^{++} + H^{+} + HCO{\cdot} && (2)\\
HCO{\cdot} + Co^{+++} &\longrightarrow Co^{++} + H^{+} + CO && (3)\\
HCO{\cdot} + H_2O &\longrightarrow HCHO + OH{\cdot} && (4)\\
&\longrightarrow HCO_2H + H{\cdot} && (5)\\
OH{\cdot} + HCHO &\longrightarrow H_2O + HCO{\cdot} && (6)\\
&\longrightarrow HCO_2H + H{\cdot} && (7)\\
H{\cdot} + H_2CO &\longrightarrow H_2 + HCO{\cdot} && (8)
\end{aligned}$$

This scheme gives for the rate of loss of cobaltic ion

$$-d[Co^{+++}]/dt = k_1[HCHO][Co^{+++}] + k_2[HCO{\cdot}][Co^{+++}]$$

and by using the usual stationary-state method for intermediates this rate expression becomes

$$-d[Co^{+++}]/dt = k_1[HCHO][Co^{+++}] + k_1k_3[Co^{+++}]^2[HCHO]/(k_2[Co^{+++}] + k_5[H_2O])$$

which is of similar form to that of the experimental relationship. Therefore, the reaction will show a first- or second-order dependence on the cobaltic-ion concentration according as the term $k_2[Co^{+++}]/k_5[H_2O]$ is much less than or much more than unity, and this will be determined by the relative rates of reactions (3) and (5).

Mechanism of Oxidation of Alcohols.—Superficially the oxidation of methyl alcohol appears to be considerably simpler than that of the higher alcohols, and the second-order velocity of reaction indicates that the measured process is

$$(1)\quad MeOH + Co^{+++} \longrightarrow MeO{\cdot} + H^{+} + Co^{++} \quad (k_1)$$

which gives as rate equation

$$-d[Co^{+++}]/dt = k_1[Co^{+++}][MeOH]$$

However, the presence of the short induction period, the effect of acid concentration on the rate, and the non-linear dependence of $\log_{10} k$ upon $1/T$ militate against the above simple scheme.

The reduction in velocity constant when the acid concentration is raised from 5N- to 10N-sulphuric acid may be a genuine effect of change of medium on the rate, or it may imply that in addition to the reaction of the cobaltic ion with methyl alcohol there is also a reaction with the methoxide ion. The ionic product of methyl alcohol is very small; Hammett ("Physical Organic Chemistry," McGraw Hill, 1940, p. 256) gives the value $K_{MeOH} = 10^{-16\cdot7}$, and thus at the high acidity used the methoxide-ion concentration would be of the order of 10^{-17}M. If then the reaction between this ion and the cobaltic ion plays any part its rate constant must be very large indeed, compared with that for the methyl alcohol–cobaltic ion reaction. On the other hand, methyl alcohol is a weak proton acceptor and consequently in strongly acid solution it is possible that the reaction

$$MeOH + OH_3^{+} \longrightarrow MeOH_2^{+} + H_2O$$

may occur and maintain an appreciable proportion of the methyl alcohol in the "methoxonium" state. If this is so and if the "methoxonium" ion, in view of its charge, reacts less readily with the cobaltic ion than does the neutral molecule then this would present an alternative explanation of the decrease in rate when the acid concentration is raised.

The occurrence of these processes introduces the additional reaction (*a*) or (*b*)

$$\begin{aligned}
(a)\quad MeO^{-} + Co^{+++} &\longrightarrow MeO{\cdot} + Co^{++} \quad (k_3)\\
(b)\quad MeOH_2^{+} + Co^{+++} &\longrightarrow MeO{\cdot} + 2H^{+} + Co^{++} \quad (k_3)
\end{aligned}$$

so that

$$-d[Co^{+++}]/dt = k_1[Co^{+++}][MeOH] + k_3[Co^{+++}][MeO^{-}] \text{ (or } + k_3[Co^{+++}][MeOH_2^{+}])$$

making the observed first-order constant, k:

$$\begin{aligned}
\text{either}\quad k &= k_1[MeOH] + k_3[MeO^{-}]\\
\text{or}\quad k &= k_1[MeOH] + k_3[MeOH_2^{+}]
\end{aligned}$$

Thus if, as is probable, k_3 or k_3 possessed different temperature coefficients from k_1 then $\log_{10} k$ would not show linear dependence on $1/T$.

As a complete reaction sequence leading to the production of formic acid the following is the simplest which can be envisaged (excluding for the moment any contribution of MeO^- or $MeOH_2^+$)

$$MeOH + Co^{+++} \longrightarrow MeO\cdot + H^+ + Co^{++}$$
$$MeO\cdot + H_2O \rightleftharpoons MeOH + OH\cdot$$
$$MeO\cdot + Co^{+++} \longrightarrow HCHO + H^+ + Co^{++}$$

followed by the sequence of reactions given in the previous section for the oxidation of formaldehyde to formic acid. Treatment of this scheme by the stationary-state method leads to a complex rate equation which can with reasonable assumptions be reduced to the simple form found experimentally.

The close similarity of the kinetic results of ethyl and propyl alcohol makes it clear that the mechanisms in the two cases must be essentially the same. As regards the products of oxidation, those of *n*-propyl alcohol have not been studied, but with ethyl alcohol oxidised by a considerable excess of cobaltic sulphate, Swann and Xanthakos (*J. Amer. Chem. Soc.*, 1931, **53**, 400) showed that acetaldehyde and acetic acid were produced together with some 4% of carbon dioxide. It is a reasonable assumption, in view of the similar kinetics, that with *n*-propyl alcohol the products will be only *n*-propaldehyde and *n*-propionic acid.

A relatively simple reaction scheme applicable to either ethyl or *n*-propyl alcohol (by making the appropriate substitutions) which leads to these products is the following :

$$C_2H_5\cdot OH + Co^{+++} \longrightarrow C_2H_4O\cdot + H^+ + Co^{++}$$
$$C_2H_4O\cdot + H_2O \rightleftharpoons C_2H_5\cdot OH + OH\cdot$$
$$C_2H_4O\cdot + Co^{+++} \longrightarrow CH_3\cdot CHO + H^+ + Co^{++}$$

followed by a sequence of reactions in which acetaldehyde is oxidised to acetic acid. The latter reaction has not been studied, although it is known from investigation of the trace-metal catalysed oxidation in the presence of molecular oxygen (Bawn and Williamson, unpublished results) that the reaction

$$CH_3\cdot CHO + Co^{+++} \longrightarrow CH_3\cdot CO\cdot + H^+ + Co^{++}$$

is highly probable. Further examination of these reactions is being carried out, and a detailed reaction scheme must await the accumulation of knowledge of the elementary reactions and the stoicheiometry relationships for the overall reaction.

Conclusions.

From this preliminary survey it is possible to draw a few simple conclusions about the reactions of the cobaltic ion with aldehydes and alcohols. In spite of the varied and complex kinetic features of the reactions it appears that they possess a certain similarity. The primary step in all cases appears to be an electron transfer between the cobaltic ion and the organic compound (or complex with the metal ion) with the generation of a free radical. The radical thus produced may then react with the solvent, the original organic compound, a further radical, or a cobaltic ion, the observed kinetics depending on the relative rates of these processes. It is also apparent that, wherever reaction between cobaltic ion and an ionised form of the organic compound (*e.g.*, formate ion) is possible, this is the preferred initial step, the rates of the reactions with ionised forms being enormously greater than those of neutral molecules.

The University, Liverpool. [*Received, July 25th*, 1950.]

78. *The Hydrolysis of Ferric Iron in Sulphate Solution.*

By T. V. Arden.

Ferric sulphate hydrolyses in three stages, to $FeOH^{++}$, $Fe(OH)_2^+$, and a precipitate whose composition varies according to the dilution. The reaction constants for the formation of $FeOH^{++}$ and $Fe(OH)_2^+$ have been found from pH measurements to be $K_1 = 1{\cdot}25 \times 10^{-3}$ $K_2 = 4{\cdot}2 \times 10^{-4}$ at 25°. There is evidence for the presence in solution of an acid complex, which may be ferrisulphuric acid, $(FeOH)(HSO_4)_2$.

The immediate reaction of sodium hydroxide with ferric sulphate solution gives an unstable solution containing high concentrations of the basic ions. When the ratio NaOH : Fe exceeds 0·5 : 1, a precipitate of $2Fe_2O_3,SO_3$ is formed, precipitation being complete when the ratio is 2·5 : 1. The addition of more sodium hydroxide causes the conversion of this precipitate into ferric hydroxide. On storage, solutions having a ratio of less than 0·5 : 1 deposit ferric oxypentasulphate [ferric (2 : 5)sulphate], $2Fe_2O_3,5SO_3$, which is stable for long periods. The precipitate of $2Fe_2O_3,SO_3$ [ferric (2 : 1)sulphate] is slowly dehydrated, and then hydrolyses further during several months to give ferric octaoxysulphate [(3 : 1)sulphate], $3Fe_2O_3,SO_3$. The ferric hydroxide precipitate is stable for an indefinite period at less than pH 7·0. In the presence of excess of sodium hydroxide, it is slowly dehydrated, to form goethite, $2Fe_2O_3,H_2O$. The effect of concentration on the titration results are discussed.

The formation of ferric hydroxide as a result of the action of alkali hydroxides on ferric salts has been studied by many workers, and values for the solubility product varying from 10^{-35} to 10^{-39} have been found. These values have usually been calculated on the assumption that ferric hydroxide is formed by the direct combination of ferric and hydroxyl ions, the solubility product therefore being given by $K = [Fe^{+++}][OH^-]^3$. Kriekov and Awzsjewitsch (*Z. Elektrochem.*, 1933, **39**, 884), by potentiometric titration of ferric sulphate with sodium hydroxide, found that the value for K varied throughout the titration; but Evans and Prior (*J.*, 1949, S157), by a similar method using ferric ammonium sulphate, obtained values which were independent of concentration. Both these groups of workers found that the first precipitation occurred late in the titration, after more sodium hydroxide had been added than was required to neutralise the free sulphuric acid present. The same observation was made by Britton (*J.*, 1925, **127**, 2148), from experiments in chloride solution. The significance of this observation does not appear to have been generally realised. For example, in the work of Evans and Prior (*loc. cit.*), the concentration of ferric ions, $[Fe^{+++}]$, was assumed to be equal to the ferric-iron concentration at the point of precipitation. Since this point represented the addition of approximately 1·2 molecules of sodium hydroxide for each atom of iron, after the removal of free acid, this assumption cannot be justified. The direct reaction between ferric and hydroxyl ions would lead to precipitation of ferric hydroxide as soon as free acid had been removed (Point *A*, Fig. 1). The formation of clear solutions after the addition of sodium hydroxide beyond this point can be explained only by the presence of soluble ions, a colloidal hydroxide or a basic salt. In each of these cases, the concentration of ferric ions would be considerably less than the total iron concentration, and the calculated value for $K_{Fe(OH)_3}$ would be correspondingly in error.

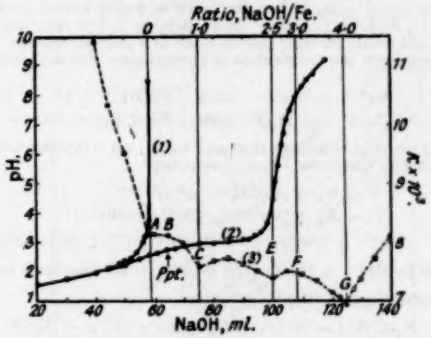
It was found by the author (unpublished work at the Chemical Research Laboratory, 1948) that the action of sodium hydroxide on ferric sulphate solutions results in the formation of a series of basic ions, followed by the precipitation of ferric pentaoxysulphate [(2 : 1)sulphate], $[Fe_2(OH)_8]_2SO_4$. The formation of this compound was complete at pH 3·0, in M/60-solution, the further addition of sodium hydroxide causing its conversion into ferric hydroxide in the pH range 3·0—8·0. Ferric hydroxide was thus not in equilibrium with Fe^{+++} and OH^- ions, and the concept of a solubility product for it was therefore considered to be without meaning. A repetition of the work of Evans and Prior, using both potentiometric and conductimetric titrations, showed that the same reaction mechanism occurred under the conditions of their experiments.

Experimental.

In a typical experiment, a solution of ferric ammonium sulphate was prepared from "AnalaR" ferric alum, together with a known quantity of free sulphuric acid. The solution was 1·0017M/30 with

respect to Fe^{+++}, 0·339M/10 with respect to NH_4^+, and 1·116M/20 with respect to free sulphuric acid. The calculated quantities of 0·1000N/10-sodium hydroxide for the titration with 50 ml. of this solution were : 58·3 ml. for neutralisation of free acid, 50·1 ml. for formation of $Fe(OH)_3$ (total 108·4 ml.), and 16·7 ml. for the formation of NH_4OH (overall total, 125·1 ml.). Two titrations were carried out simultaneously, at 25·0° ± 0·02°, the pH being measured by means of a glass electrode in conjunction with a saturated calomel half-cell in one case, and, in the other case, the conductivity being measured by means of a dip-type electrode system with a Mullard universal measuring bridge at 1000 cycles. A titration of 50 ml. of 1·116M/20-sulphuric acid was also carried out, with measurement of pH only. In Fig. 1, the pH curve for the ferric sulphate titration (2) falls below that for the sulphuric acid solution (1) before all free acid is removed, indicating that extensive hydrolysis takes place even in the presence of free acid. The neutralisation of free acid at *A* is not accompanied by any inflexion in the pH curve, although its position is defined by a break in the conductivity curve (3). In the region *AC* the pH rises slowly, with a corresponding reduction in conductivity, this process ending at *C*, where 75·0 ml. of sodium hydroxide solution have been added, representing a NaOH : Fe ratio of 1 : 1. The precipitation point, which has been found to vary according to the rate of titration, occurred in this case at *B*. From *C*, the pH and conductivity remain almost constant, to *E* (100·0 ml. of NaOH), where the pH rises and a conductivity minimum occurs. Chemical determinations show that precipitation of iron is complete at this point, which represents the addition of 2·49 mols. of NaOH per atom of Fe. The precipitate at this point is therefore ferric pentaoxysulphate, $[Fe_2(OH)_4]_2SO_4$ or $2Fe_2O_3.SO_3$. From this point, the conductivity of the solution rises, in spite of the reduction in hydrogen-ion concentration, owing to the conversion of the precipitate into $Fe(OH)_3$, and the consequent liberation of sulphate ions. This process is complete at about *F*, where an ill-defined conductivity maximum is followed by decreasing conductivity in the region *FG*, as ammonium sulphate is converted into ammonium hydroxide. The minimum at *G* (125 ml. of NaOH) agrees with the calculated end-point for the overall reaction, the subsequent sharp rise in conductivity being due to the addition of excess of sodium hydroxide.

FIG. 1.



It is inferred from this preliminary experiment that the formation of ferric hydroxide occurs in at least three stages. The first involves the formation of a soluble complex containing one hydroxyl group for each iron atom, and may be written

$$Fe^{+++} + H_2O \rightleftharpoons FeOH^{++} + H^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

This reaction was first proposed by Goodwin (*Z. physikal. Chem.*, 1896, **21**, 1), and has been studied by Lamb and Jacques (*J. Amer. Chem. Soc.*, 1938, **60**, 1215) and by Bray and Herskey (*ibid.*, 1934, **56**, 1899), who found the reaction constant to be $2·5 \times 10^{-3}$ and $4·9 \times 10^{-4}$, respectively.

The second stage is the precipitation of ferric pentaoxysulphate, $2Fe_2O_3.SO_3$. No reaction is given for this process at this point, since it will be shown that a further hydrolysis stage occurs before the formation of the precipitate. The final process, the conversion of ferric pentaoxysulphate into ferric hydroxide, is not complete until the pH has been raised above 7·0. Since the presence of ammonium sulphate in solution complicates the interpretation of the pH and conductivity curves in the region *EG*, the use of ferric alum was discontinued, and pure ferric sulphate solutions used. The hydrolysis of ferric sulphate was studied by the measurement of the pH of solutions, containing no free acid, at concentrations varying from 2×10^{-3} to 1×10^{-4} g.-atom of Fe/l.

The Hydrolysis of Ferric Sulphate.—Attempts to prepare pure ferric sulphate by repeated recrystallisations did not result in complete removal of free sulphuric acid. Accordingly, a solution was prepared from spectrographically pure metallic iron, and a measured quantity of N-sulphuric acid ("AnalaR"). The solution was oxidised with a small excess of 100-vol. "AnalaR" hydrogen peroxide, which was first adjusted to pH 7·0. The excess of peroxide was removed by prolonged boiling, and the solution was then aged for 10 days in order to establish equilibrium between all the ions present. A small quantity of iron was deposited as a film on the glass during the boiling process. This was redissolved in hydrochloric acid, the quantity determined, and subtracted from the total weight of iron used. The stock iron solution thus prepared was 0·994M/30 with respect to iron, and 0·459M/20 with

respect to free sulphuric acid. Thus 25 ml. of this solution required 10·9 ml. of 0·1054N-sodium hydroxide for neutralisation of free acid, and the concentration of the resulting solution was $2{\cdot}29 \times 10^{-4}$ g.-atom of Fe/l. The pH of this solution was measured at 25·0°, and a series of dilutions was carried out, freshly boiled conductivity water having a pH of 6·2 being used. The presence of sodium sulphate in the ferric sulphate solution is a disadvantage of this procedure, but the method is the only one which has been found to ensure a precise knowledge of the composition of the solution. The results are shown in Table I.

TABLE I.

C.	pH.	$[H^+]$.	$[H^+]/C$.	Remarks.
$2{\cdot}29 \times 10^{-3}$	2·30	$5{\cdot}01 \times 10^{-3}$	0·219	
1·145 ,,	2·45	3·54 ,,	0·308	
$5{\cdot}725 \times 10^{-3}$	2·61	2·45 ,,	0·429	
2·863 ,,	2·78	1·66 ,,	0·579	
1·432 ,,	2·96	1·10 ,,	0·770	
$7{\cdot}16 \times 10^{-4}$	3·14	0·72 ,,	1·01	Faint cloud
3·58 ,,	3·35	$4{\cdot}46 \times 10^{-4}$	1·25	Precipitate
1·79 ,,	3·48	3·30 ,,	1·85	,,
$8{\cdot}95 \times 10^{-5}$	3·73	1·86 ,,	2·07	,,
4·47 ,,	4·04	$9{\cdot}10 \times 10^{-5}$	2·04	,,
2·24 ,,	4·32	4·78 ,,	2·13	,,
1·12 ,,	4·63	2·36 ,,	2·12	,,

The value $[H^+]/C$ representing the number of hydrogen ions produced by 1 atom of iron, approaches a maximum value of approximately 2·1 at zero concentration. Since this experiment was carried out very rapidly, in order to minimise the effect of the precipitation stage of hydrolysis, the results would suggest the formation of $Fe(OH)_2^+$ as the last soluble product of hydrolysis. The possible single-stage hydrolysis processes, which could occur before the point of precipitation, include the direct formation from Fe^{+++} ions of $FeOH^{++}$, $Fe(OH)_2^+$, Fe_2O^{4+}, or $Fe_2(OH)_2^{4+}$. The reaction constant of each of these processes was calculated, and found in each case to vary in a regular manner with pH. None of these processes, therefore, can represent the mechanism of hydrolysis. The simplest two-stage process which can be postulated is

$$Fe^{+++} + H_2O \rightleftharpoons FeOH^{++} + H^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$FeOH^{++} + H_2O \rightleftharpoons Fe(OH)_2^+ + H^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The relation between hydrogen-ion concentration and total iron concentration can be calculated from the following equations, activity coefficients being neglected :

$$K_1 = [FeOH^{++}][H^+]/[Fe^{+++}]$$

$$K_2 = [Fe(OH)_2^+][H^+]/[FeOH^{++}]$$

$$[Fe^{+++}] + [FeOH^{++}] + [Fe(OH)_2^+] = C \text{ (total iron)}$$

and $$3[Fe^{+++}] + 2[FeOH^{++}] + [Fe(OH)_2^+] + [H^+] = 3C \text{ (electrical neutrality)}$$

Elimination of $[Fe^{+++}]$, $[FeOH^{++}]$, and $[Fe(OH)_2^+]$ gives

$$K_1(C[H^+] - [H^+]^2) + K_1K_2(2C - [H^+]) = [H^+]^3 \quad . \quad . \quad . \quad . \quad . \quad (3)$$

The results of Table I have been used to calculate values for K_1 and K_2, with the results given in Table II.

TABLE II.

$C \times 10^3$.	$K_1 \times 10^3$.	$K_2 \times 10^4$.
22·9		
11·45	1·15	5·20
5·725	1·32	3·68
2·863	1·28	3·68
1·432		
Mean	1·25	4·2

Equation (3) can be rearranged as follows :

$$C = \frac{[H^+]^3 + K_1[H^+]^2 + K_1K_2[H^+]}{K_1[H^+] + 2K_1K_2}$$

By substituting the values calculated for K_1 and K_2, a theoretical dilution curve has been calculated, and is given as the upper continuous line in Fig. 2. The observed values from Table I have been plotted as circles, which fall on the theoretical curve well beyond the region which was used for the calculation of K_1 and K_2. These values fall below the calculated curve only when the hydrolysis mechanism has been changed by the formation of a solid phase.

The effect of this third stage of hydrolysis was investigated by measuring the pH at each concentration over a period of several days. The resultant curves, which are shown in Fig. 2, are remarkable in assuming a sigmoid form, the significance of which will be discussed in conjunction with the titration results of Fig. 4. Considering at present only the upper portions of each curve, it is seen that with increasing time, the curves tend to approach the lower continuous curve at an increasingly high concentration. If the third stage of hydrolysis in dilute solution is given by the equation

$$Fe(OH)_2^+ + H_2O \longrightarrow Fe(OH)_3\downarrow + H^+$$

then

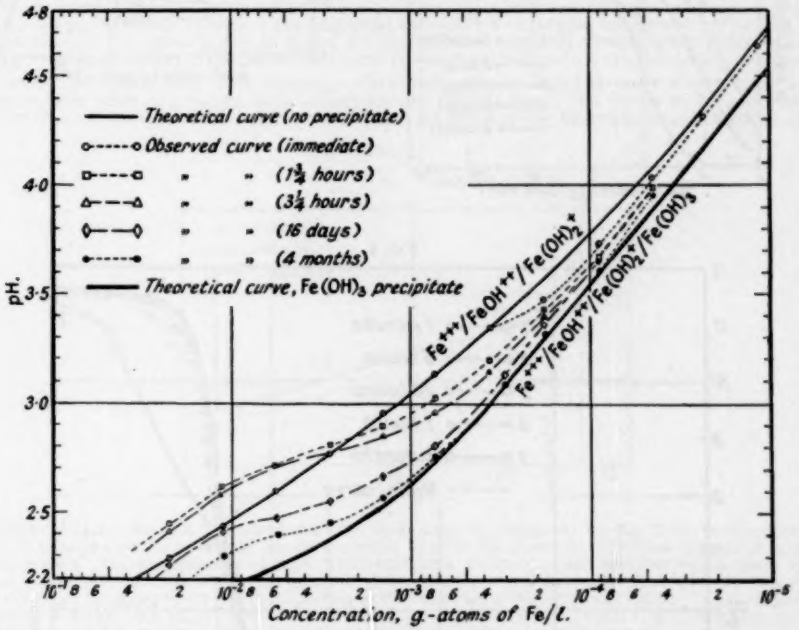
$$K_3 = [H^+]/[Fe(OH)_2^+]$$

By a reasoning similar to that used for equation (3), it can be shown that

$$K_1K_2K_3(3C - [H^+]) = 3[H^+]^3 + 2K_1[H^+]^2 + K_1K_2[H^+] \quad . \quad . \quad . \quad . \quad . \quad (4)$$

On substituting the values previously determined for K_1 and K_2, and the single value pH = 3·09 when

FIG. 2.



$C = 3·575 \times 10^{-4}$, taken from the final observed curve of Fig. 2, K_3 is found to be 95. Equation (4) then becomes

$$5·0 \times 10^{-6}(3C - [H^+]) = 3[H^+]^3 + 2·5 \times 10^{-3}[H^+]^2 + 5·25 \times 10^{-7}[H^+] \quad . \quad . \quad . \quad (5)$$

The lower continuous line in Fig. 2 is a curve calculated from equation (5). The agreement with the observed curves is good in solutions more dilute than 10^{-3} g.-atom of Fe/l. In more concentrated solutions, the observed pH values fell above the calculated curve. It is shown below, in the consideration of titration results, that this phenomenon is due to the formation of a basic sulphate, ferric oxypentasulphate [(2 : 5)sulphate], $2Fe_2O_3.5SO_3$, as the solid product of hydrolysis at concentrations higher than 10^{-3} g.-atom of Fe/l.

The results of these dilution tests demonstrate that the complete hydrolysis of ferric sulphate is a slow process, and pH measurements vary according to the moment of determination. A study of the reactions of ferric sulphate must therefore include the effect of time, and a normal titration technique, even if carried out at a known rate, must lead to false conclusions, since the observations are made progressively later as the titration proceeds, and the solutions are in correspondingly different equilibrium states.

To overcome this difficulty, the technique of the static titration was used, separate flasks each containing 25 ml. of ferric sulphate solution being treated with quantities of 0·1054N-sodium

FIG. 3A.

Quantity of iron precipitated.

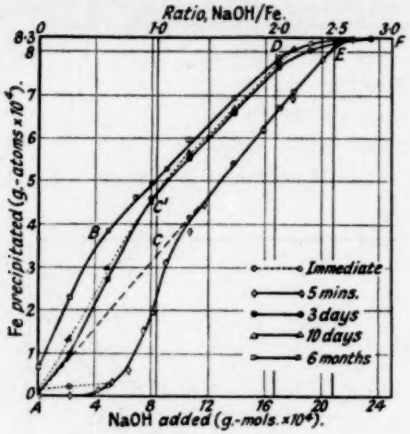


FIG. 3B.

Ratio SO_4/Fe.

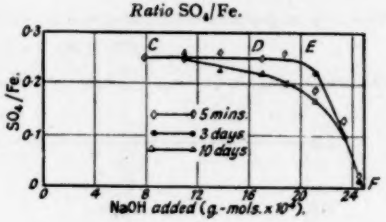
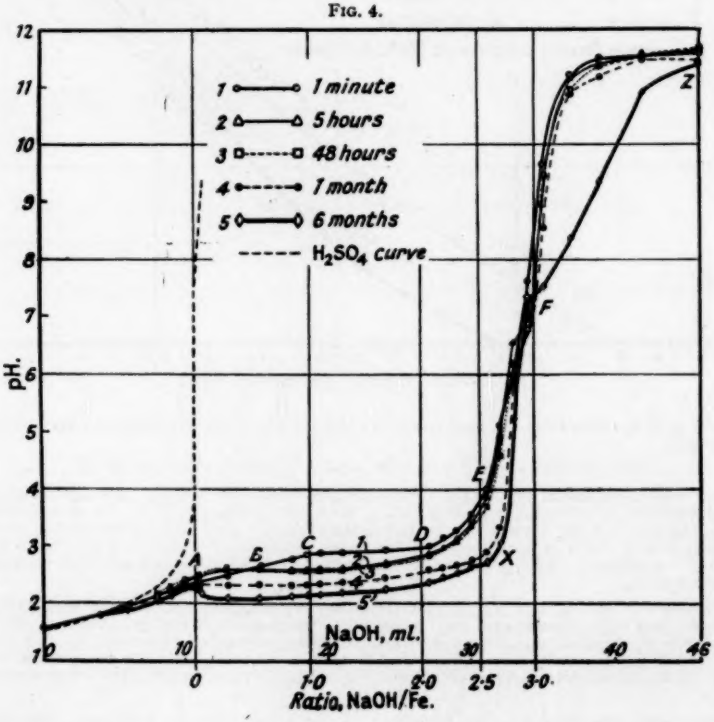


FIG. 4.

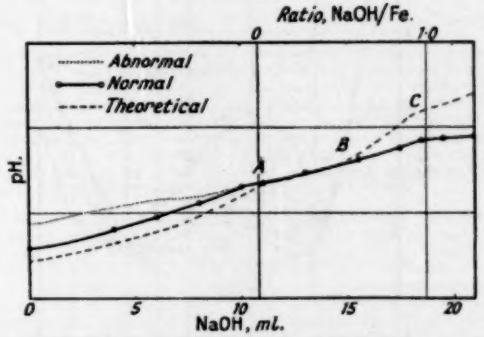


hydroxide solution varying from 0 to 46·0 ml. The titration was carried out in 26 steps, six identical series being prepared. Two were used for measurements of pH and conductivity, severally, over a period of 6 months, and the other four were centrifuged after different time intervals, for the determination of the quantity of the iron precipitated, and the analysis of the precipitates. For convenience in reference, Figs. 3—9, giving the results of these titrations, have all been lettered in the same manner. The start of the titration is represented by point *O*, where no sodium hydroxide is added. Point *A*, at 10·9 ml., represents the calculated end of free acid; *B* = 14·8 ml. (NaOH/Fe = 0·5); *C* = 18·8 ml. (NaOH/Fe = 1·0); *D* = 26·6 ml. (NaOH/Fe = 2·0); *E* = 30·6 ml. (NaOH/Fe = 2·5); and *F*, at 34·5 ml. (NaOH/Fe = 3·0), represents the calculated complete formation of ferric hydroxide or oxide.

A study of the precipitation curves (Fig. 3), the pH curves (Fig. 4), and the conductivity curves (Fig. 6) shows that the reaction of sodium hydroxide with ferric sulphate takes place in three periods of time, which have been termed the initial, intermediate, and final equilibrium stages. The initial stage is of some minutes' duration, after which a steady change takes place in all parts of the titration, to establish the intermediate stage after about 24 hours. The stability of this stage is shown by the precipitation curves (Fig. 3) which, after a considerable change from the early results, are almost unchanged between 3 and 10 days, by the pH curves, which are identical at 5 and at 48 hours, and by the conductivity curves, which preserve a constant form between 5 and 48 hours, although a small overall increase occurs in this time. The final stage, reached in 4—6 months, is characterised by further modifications in the curves of Figs. 3, 4, and 6. Each of these equilibrium stages is also characterised by clearly-defined changes in the physical form and chemical reactivity of the precipitates and solutions.

Initial Equilibrium Stage (1—5 *Minutes*).—The initial curves in Figs. 3, 4, and 6 were plotted from measurements made one minute after mixing each of the solutions. The liquors in the region *AB* contained small traces of solids which formed round the drops of the sodium hydroxide solution and

FIG. 5.



redissolved during the first five minutes to give clear, deep red solutions. In Fig. 3, the total quantity of iron precipitated (in g.-atoms) has been plotted against the quantity of sodium hydroxide added (in g.-mols.). The precipitation of ferric hydroxide from the start of the titration would result in a straight line *AF*, of slope 0·333. The curves observed after 1 and 5 minutes show that the delay in precipitation occurring in the region *AB*, owing to the formation of $FeOH^{++}$ and $Fe(OH)_2^+$ ions, is followed between *B* and *C* by a rapid increase in the quantity of iron deposited. From *C* to *E* the quantity of precipitate, which at this stage is brown and gelatinous, increases proportionally to the amount of sodium hydroxide added, along a curve which, if produced in the direction *EC*, passes through the origin. The slope of the straight line *CE* is 0·405, or 2·02/5, indicating that 2 atoms of iron are precipitated by 5 molecules of sodium hydroxide. It is thus evident that the overall process resulting immediately from the addition of sodium hydroxide solution to ferric sulphate solution consists of, first, the production of an unstable solution containing an abnormally high proportion of the basic ions $FeOH^{++}$ and $Fe(OH)_2^+$, and secondly, the breakdown of this solution by the addition of more sodium hydroxide, to form ferric pentaoxysulphate, by a reaction of the type

$$4Fe(OH)_2^+ + SO_4^= + 2H_2O \longrightarrow [Fe_2(OH)_4]_2SO_4\downarrow + 2H^+ \quad . \; . \; . \; . \; (6)$$

This process is complete at *E*, when the NaOH/Fe ratio is 2·5. No iron can then be detected in solution.

The analyses of the precipitates at points in the titration between *C* and *F* (Fig. 3, *B*) give some confirmation of this mechanism. Analytical results must be treated with caution, since the process of filtration and washing can, if prolonged, lead to considerable hydrolysis of the precipitate, with the loss of sulphate. Nevertheless, the results shown in Fig. 3B indicate that the ratio SO_4 : Fe in the precipitate approximates to 0·25 throughout the region *CE*, after which it falls to zero at *F*. This agrees with the postulate of an initial precipitate of ferric pentaoxysulphate, $[Fe_2(OH)_4]_2SO_4$, which is converted into ferric hydroxide in the region *EF*, by the action of more sodium hydroxide. It is noticeable that the precipitate becomes darker, as sulphate is removed, until in the region *FZ* it is in the dark red-brown form which is observed in the analytical precipitation of ferric hydroxide.

pH *Changes in the Initial Equilibrium Stage.*—Measurements of pH were made by means of a glass electrode in conjunction with a dip-type calomel half-cell. The electrode system was standardised before and after each set of readings at pH 3·97 and 9·18, freshly prepared phthalate and borate buffers being used. The agreement between the four standardisation readings was always within pH 0·05, and usually within pH 0·02. Curve 1 of Fig. 4, measured after 1 minute, is similar to those recorded by Britton, and by Evans and Prior, and is characterised by three distinct sections: *OAC*, where little precipitation occurs, and the pH rises steadily, *CD*, where the pH remains constant, and *DEF*, in which the curve again rises rapidly. In the region *OAB*, before precipitation occurs, the pH–volume relationship is governed by the first two hydrolysis stages of the ferric ion, for, from the equations for K_1, K_2, and C (p. 352) and

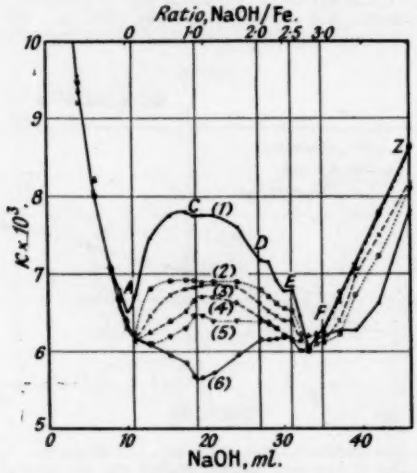
$$[H^+] = [FeOH^{++}] + 2[Fe(OH)_2^+] - [B]$$

where [B] represents the concentration of added alkali, we have

$$C = \frac{([H^+] + [B])([H^+]^2 + K_1[H^+] + K_1K_2)}{K_1([H^+] + 2K_2)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

Equation (7) is of general application; in the particular case of this titration, with the values of K_1 and K_2 in Table II we have $C = 0{\cdot}0329 \times 25/(25 + v)$, where v = the volume of sodium hydroxide added.

FIG. 6.



(1) 6 *months.* (2) 2 *months.* (3) 13 *days.*
(4) 48 *hours.* (5) 5 *hours.* (6) 1 *minute.*

Moreover, since [B] = 0 when $v = 10{\cdot}9$, [B] = $0{\cdot}1054(v - 10{\cdot}9)/(25 + v)$. These values being substituted in equation (7), it can be shown that

$$[H^+]^3(25 + v) + [H^+]^2(0{\cdot}107v - 1{\cdot}11) + [H^+](1{\cdot}31v - 24{\cdot}3) \times 10^{-4} + 5{\cdot}25 \times 10^{-7}(0{\cdot}1054v - 2{\cdot}78) = 0 \quad . \quad . \quad . \quad (8)$$

Equation (8) has been used to calculate a theoretical titration curve, which is shown together with the observed initial curve in Fig. 5. The agreement between the two curves is good in the region *AB*, but the c lculated results are too low in the presence of free acid. The effects of activity and of the presence of HSO_4^- ions, both of which would tend to raise the observed pH, have not been considered in arriving at equation (8), and might account for this difference. There is also some evidence for the formation of an acid complex of ferric sulphate, whose presence would also tend to raise the observed pH.

Ferrisulphuric Acid.—The ferric sulphate solution used for the titration shown in Fig. 4 was aged for some days before use. It has been found that similar titrations carried out on identical freshly prepared solutions frequently give higher pH values in the region *OA*. The elevation is variable, according to the age and manner of preparation of the solution, and the effect normally disappears after one or two days. The maximum elevation of this type which has been observed is recorded in Fig. 5 (dotted line). The pH values in the presence of free acid are higher than those given by the same concentration of sulphuric acid in the absence of iron, and indicate the removal of sulphuric acid from the solution by the formation of an acid ferric sulphate. No evidence for the composition of such a compound can be

deduced from this work. The existence of the compound, $Fe_2O_3,4SO_3$, in the solid state is, however, well known. It occurs as the mineral rhomboclase, $Fe_2O_3,4SO_3,9H_2O$, and its presence as a solid phase in contact with acid solutions of ferric sulphate has been demonstrated by Applebey and Wilkes (*J.*, 1922, **121**, 337) and others by phase-rule studies. Recoura (*Compt. rend.*, 1911, **153**, 1223) considered it to be ferrisulphuric acid, $Fe(OH)(HSO_4)_2$, and prepared the ethyl and other esters. It is suggested that this compound may be formed to an undefined extent in acid solutions of ferric sulphate. The presence of such an acid salt would raise the pH in the region *OA*, and give a further reason for the variation between observed and calculated pH values.

The Mechanism of Precipitation.—The initial pH curve (Fig. 4) is divided into 4 sections, *AC*, *CD*, *DE*, and *EF*, the positions of *A*, *C*, *D*, and *E* being confirmed by inflexions on the corresponding conductivity curve (Fig. 6). The most obvious explanation of these inflexions would be the formation of $Fe(OH)SO_4$ in the region *AC*, followed by its conversion into $[Fe(OH)_2]_2SO_4$ and $[Fe_2(OH)_4]_2SO_4$ in the regions *CD* and *DE*. This process would, however, involve the complete removal of iron from solution at *C*. Moreover, a calculation of the acid produced during the further hydrolysis to the final state (Fig. 4) shows that this value is much less than would occur were the precipitate $Fe(OH)SO_4$ or $[Fe(OH)_2]_2SO_4$, but agrees well with the initial formation of $[Fe_2(OH)_4]_2SO_4$ at all points in the titration.

The titration results can be explained by a consideration of the processes in solution leading up to precipitation. In the region *AD*, the primary process has been shown to be the production of increasing quantities of the basic ions $Fe(OH)^{++}$ and $Fe(OH)_2^+$, followed by the formation of a precipitate. The inflexion in the pH curve at *C* is caused by the rapid increase in the total quantity of precipitate occurring at this point (cf. Fig. 3), while the horizontal section *CD* agrees with the concept that hydrolysis in solution is taking place simultaneously with precipitation. If the precipitation reaction were the only one occurring, the pH curve would rise at a rate governed by the solubility product of the precipitate. In the region *DE*, the mechanism changes. In the absence of a precipitate, the whole of the iron present at *D* would be converted into $Fe(OH)_2^+$; thus the precipitate may be considered as being formed from a solution of uniform ionic type, by the reaction

$$4Fe(OH)_2^+ + 2SO_4^{--} + 2NaOH \longrightarrow [Fe_2(OH)_4]_2SO_4 \downarrow + Na_2SO_4 \quad . \quad . \quad (9)$$

In this region, therefore, the pH is governed by the solubility product of ferric pentaoxysulphate, $K = [Fe(OH)_2^+]^4[SO_4^{--}][OH^-]^2$, and thus rises rapidly as $[Fe(OH)_2^+]$ is reduced to zero at *E*. The overall process of precipitation in the initial equilibrum stage may thus be considered as (i) hydrolysis in solution from *A* to *C*, with formation of $FeOH^{++}$ and $Fe(OH)_2^+$, and a corresponding rise in pH, (ii) further hydrolysis, together with precipitation from *C* to *D*, at constant pH, (iii) precipitation from a completely hydrolysed solution from *D* to *E*, with rapidly rising pH, (iv) conversion of the basic sulphate into ferric hydroxide from *E* to *F*, the rate of rise of pH increasing. This mechanism represents an oversimplified picture of the process, in which the reactions of each section are in practice somewhat modified by the preceeding and succeeding sections.

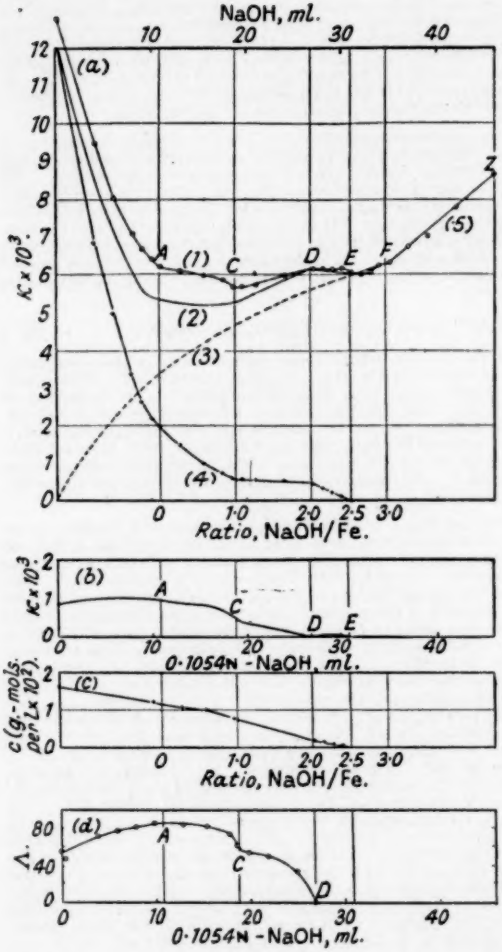
Conductivity Changes in the Initial Equilibrium Stage.—Conductivities were measured 1 minute after the solutions had been mixed, a dip-type electrode system being used in conjunction with a Mullard universal measuring bridge. The initial conductivity curve (Fig. 6) is notably different from those measured later, the conductivities in the region *AF* being very low, with a minimum at *C*. The conductivity curves have been analysed, by the calculation of the conductivities of all the ions present other than those of iron and its associated sulphate. The conductivity of the sodium sulphate formed at each stage of the titration was measured by a series of conductimetric titrations, each of 25 ml. of sulphuric acid, of varied concentration, with 0·1054N-sodium hydroxide. The minima of these titrations were plotted against the volumes of sodium hydroxide added at the minimum points. In the last of these titrations, this volume was 34·6 ml., and in this case the alkaline portion of the curve gave the total conductivity of sodium hydroxide and sodium sulphate in the region *FZ*. The curves for $\kappa_{Na_2SO_4}$ and for $\kappa_{(NaOH + Na_2SO_4)}$, which are common to all periods, have been plotted in Figs. 7—9 as broken and continuous lines respectively. The total conductivity of the sulphuric acid present at any point, including both the free acid and that formed by hydrolysis, has been calculated by assuming (i) $pH = \log a_H^{-1}$, (ii) $\kappa = 0{\cdot}430a_H$ ($\Lambda_{\infty,H_2SO_4} = 430$ at 25°). These assumptions give reasonably accurate results in the region *AF*, where $[H^+]$ is low, but the results in solutions containing high concentrations of free acid are of little value. The continuous curves in Figs. 7*a*—9*a* give the total conductivity of all ions other than those of ferric sulphate, *i.e.*, $\kappa_{(Na_2SO_4 + H_2SO_4)}$ in the region *OAF*, and $\kappa_{(Na_2SO_4 + NaOH)}$ in the region *FZ*. These curves therefore represent the "salt line" of the titration. The differences between them and the observed curves give the variation of the apparent specific conductivities of the ferric sulphate solutions (Figs. 7*b*—9*b*). By comparison with the measured concentration of the ferric sulphate remaining in solution (Figs. 7*c*—9*c*), the apparent molar conductivities of the ferric sulphate remaining in solution have been calculated by the expression $\Lambda = \kappa/c \times 1000$. These values are undoubtedly affected to some extent by the occlusion of sodium sulphate on to the precipitates; nevertheless, the curves yield valuable information on the changes taking place in solution.

Fig. 7 gives the analysis of the initial curve of Fig. 6. The observed conductivity curve has been correlated at all stages with the changes in conductivity due to the sulphuric acid and sodium sulphate present. The apparent molecular conductivity (Fig. 7*d*) of the ferric sulphate remaining in solution is at a maximum at *A*, decreasing rapidly to zero at *D*, along a curve which is inflected at *C*. This observation is in accordance with the concept of hydrolysis in solution in two stages, to give increasing quantities of poorly-conducting basic ions. The apparent value of zero at *D* would indicate that the $Fe(OH)_2^+$ ion is non-conducting, but it is probable that the observed conductivity has been reduced by the occlusion of soluble salts by the precipitate. Nevertheless, the rapid decrease in the molar conductivity from *C* to *D* shows that the true molar conductivity of the basic ion is low. From *D*, the

observed specific conductivity of the solution (Fig. 7*a*) follows the salt line closely, little change in conductivity resulting from the conversion of $Fe(OH)_3^{+}$ ions into insoluble ferric pentaoxysulphate, while from *E* to *F*, the observed conductivity rises with the salt line, as sulphate is extracted from the precipitate. In the presence of excess of alkali, the observed curve follows the NaOH–Na_2SO_4 curve, showing that, apart from a small degree of occlusion of soluble salts on the precipitate, no further action takes place in alkaline solution.

The Intermediate Equilibrium Stage.—During the first 4—5 hours after mixing, marked changes

FIG. 7.



(*a*) *Conductivity immediate.*
(1) $\kappa_{(obs.)}$.
(2) $\kappa_{(Na_2SO_4 + H_2SO_4)}$.
(3) $\kappa_{(Na_2SO_4)}$.
(4) $\kappa_{(H_2SO_4)}$.
(5) $\kappa_{(NaOH + Na_2SO_4)}$.

(*b*) *Apparent* $\kappa_{Fe_2(SO_4)_3}$. $\kappa_{(obs.)} - \kappa_{(Na_2SO_4 + H_2SO_4)}$.

(*c*) *Concentration of dissolved* $Fe_2(SO_4)_3$.

(*d*) *Apparent molecular conductivity of* $Fe_2(SO_4)_3$.

occur in all the solutions forming the titration. The changes are largely complete after 24 hours, and the appearance of the precipitates, together with the pH and conductivity curves which demonstrate the reactions in solution, then show little further change for some days. This intermediate condition then breaks down gradually, during some months, to the final stage. The intermediate stage is characterised by a large increase in the quantity of precipitate occurring throughout the titration (Fig. 3*a*), together with fundamental changes in the appearances and characteristics of the precipitates. In the region *AB*, the deep red clear solutions become cloudy after 5—10 minutes, and then slowly deposit precipitates which after 24—30 hours assume a characteristic bright orange, flocculent condition which is observed

nowhere else in the titration. The supernatant liquors simultaneously lose their colour, until after 24 hours they are only a pale amber. This process is accompanied by a rise in pH similar to that observed during the hydrolysis experiment (Fig. 2). The conductivity also rises in this region, in spite of the reduction in hydrogen-ion concentration, and the loss of iron by precipitation. From *B* to *E*, the original gelatinous red-brown precipitate changes to a yellow powder, with an increase in the total quantity of precipitate, together with corresponding increases in hydrogen-ion concentration and conductivity. In the region *EF*, the original dark brown gelatinous precipitates are unchanged, and little difference is observed from the original pH and conductivity curves. From *F* to *Z*, where excess of alkali is present, the precipitates gradually change in form during several days, to give a drab yellow powder. This process is increasingly rapid with increasing concentration of free sodium hydroxide, and is complete after 5 days in all solutions whose pH is greater than 8·0.

The Region AB NaOH/Fe = 0—0·50).—The rise in pH in this region (Fig. 4), in spite of the formation of a precipitate, constitutes a reversal of the normal process of hydrolysis. The explanation for it is found in the nature of the precipitate, which is clearly distinguishable from that occurring in the region *BE*. The mineral copiapite, $2Fe_2O_3.5SO_3.18H_2O$, is known to be produced by hydrolysis of slightly acid solutions of ferric sulphate; and Scharizer (*Z. Krist.*, 1913, **52**, 384) considered that its formation was due to the condensation of four molecules of ferrisulphuric acid. Wirth and Bakke (*Z. anorg. Chem.*, 1914, **87**, 21), in a phase-rule study of the system Fe_2O_3–SO_3–H_2O, showed that a similar material existed in contact with solutions in which the $SO_3 : Fe_2O_3$ ratio was approximately 3 : 1. The region of formation of this compound has been defined more clearly in this work, since it has been found to occur only in those solutions characterised by rising pH values, *i.e.*, between 9·0 and 13·8 ml. of NaOH, where the $SO_3 : Fe_2O_3$ ratio is 3·2—2·5 : 1. The end of formation of this compound at *B* (NaOH/Fe = 0·5) points clearly to the structure $(Fe_2OH)_4(SO_4)_5$, or $2Fe_2O_3.5SO_3$, in agreement with the results of earlier workers. Analyses have given variable results, owing to the effects of hydrolysis during filtration and washing. The formation of this compound can be explained by either of the following reactions:

$$2FeOH^{++} + 2Fe^{+++} + 5SO_4^{=} \longrightarrow (Fe_2OH)_4(SO_4)_5 \downarrow \quad . \; . \; . \; . \; (10)$$

$$4Fe^{+++} + 6SO_4^{=} + 2H_2O \longrightarrow (Fe_2OH)_4(SO_4)_5 \downarrow + 2H^+ + SO_4^{=} \; . \; . \; . \; (11)$$

The first of these processes, by partly removing the less basic ions from solution, would result in a reversal of the hydrolysis of the $Fe(OH)_2^+$ ions, and a corresponding rise in pH. This reversal of hydrolysis would account also for the decrease in the colour of the solutions, by the decrease in the concentration of the highly coloured basic ions. Moreover, the establishment of new equilibrium conditions, with a higher proportion of the less basic ions, would account for the rise in the molecular conductivity in this region. Rabinowitch and Stockmeyer (*J. Amer. Chem. Soc.*, 1942, **64**, 335), in a study of the absorption spectra of ferric perchlorate, isolated the spectra of Fe^{+++} and $FeOH^{++}$, and found deviations from Beer's law which could be explained by the formation of Fe_2OH^{5+}. In the consideration of the final equilibrium stage, it will be shown that increases in the quantity of ferric oxypentasulphate over a period of 6 months are accompanied by a reduction in pH. During this stage, therefore, the attainment of equilibrium by reaction (10) must be followed by a slow further hydrolysis by reaction (11).

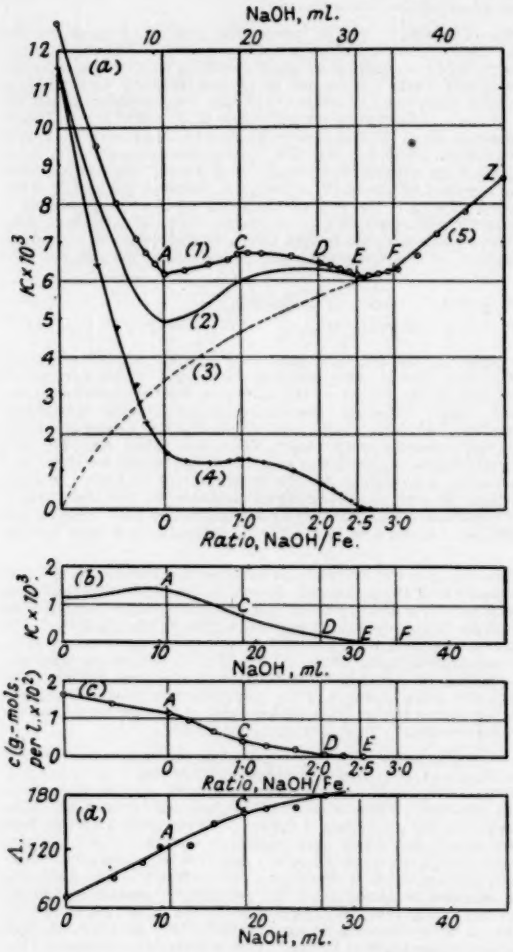
Reactions (10) and (11) can also explain the series of sigmoid curves observed during the dilution experiment (Fig. 2). It has already been shown that the precipitate formed in dilute solution (less than 10^{-3} g.-atom of Fe/l.) is ferric oxide or hydroxide. It is now apparent that in solutions more concentrated than 3×10^{-3} g.-atom of Fe/l., the precipitate is largely ferric oxypentasulphate, $2Fe_2O_3.5SO_3$. The dilution curves therefore consist of two distinct sections, each associated with one of these compounds, while the sigmoid portion represents the transition between them. There is no conclusive evidence to show whether this transition is a single process, or whether the sulphates of the ions $FeOH^{++}$ and $Fe(OH)_2^+$ occur as intermediate steps; but the sharp changes in the dilution curve make the former mechanism more probable. It is shown below that in the titration with sodium hydroxide, the transition from ferric oxypentasulphate to ferric pentaoxysulphate is almost certainly direct.

The Region BE(NaOH/Fe = 0·50—2·50).—The slimy yellow precipitate in this region can be seen to exist in three forms, light yellow, dull yellow, and dull orange, the boundaries between them being at *C* and *D*. The first of these deposits dissolves fairly readily in dilute mineral acids, whereas the second and the third are increasingly difficult to dissolve. These three deposits are associated with three approximately linear sections *AC*, *CD*, and *DE* of the precipitation curves observed after 3 and 10 days (Fig. 3), the ratio (Fe precipitated)/(NaOH added) decreasing from section to section. Point *C* is also marked by inflexions in the pH and conductivity curves (Figs. 4 and 6); but *D* is less clearly defined in these curves. The increase in hydrogen-ion concentration in the region *BE*, during the first 24 hours, is of the order to be expected from the increase in quantity of the precipitate, assuming that its composition is unchanged, and allowing for the partial reversal of hydrolysis of the basic ions remaining in solution, caused by the decrease in pH. The precipitates occurring after *E* are all coloured dark brown by the presence in them of the increasing quantities of $Fe(OH)_3$. It is therefore considered that the precipitates in the region *BE*, in the intermediate equilibrium stage, consist of ferric pentaoxysulphate, in three different physical forms, which are probably in decreasing states of hydration. The analyses of the precipitates (Fig. 3B) tend to confirm this view, since the SO_4 : Fe ratio after 3 days, as in the initial stage, is 0·25 in the region *CE*, and is then reduced to zero by the addition of sodium hydroxide in section *EF*. After 10 days, the loss of some sulphate is apparent towards the end of the region. Further confirmation of the chemical nature of the precipitate is given by a consideration of the processes leading to the final equilibrium stage (see p. 361).

Conductivity Changes in the Intermediate Stage (Fig. 6).—The increase in conductivity occurring in the first 5 hours is accompanied by a change in the form of the conductivity curve from *A* to *E*. The

minimum at *C* disappears, to be replaced by a maximum, while a second maximum appears at *D*. The curves remain constant in type for several days, although the overall level rises steadily. An analysis of the 48-hour curve from Fig. 6 is given in Fig. 8, which demonstrates that the observed inflexions can be correlated with the changes in pH and sodium sulphate concentration. The molar conductivity of the ferric sulphate remaining in solution (Fig. 8*d*), after correction for the effect of all the other ions in solution, has increased throughout the region *AE*. Moreover, this value increases in the direction *AE*, *i.e.*, with decreasing concentration of the remaining iron, instead of decreasing rapidly as was observed

FIG. 8.



(*a*) *Conductivity, 48 hours.*
(1) $\kappa_{(obs.)}$.
(2) $\kappa_{(Na_2SO_4 + H_2SO_4)}$.
(3) $\kappa_{(Na_2SO_4)}$.
(4) $\kappa_{(H_2SO_4)}$.
(5) $\kappa_{(NaOH + Na_2SO_4)}$.

(*b*) *Apparent* $\kappa_{Fe_2(SO_4)_3}$, $\kappa_{(obs.)} - \kappa_{(Na_2SO_4 + H_2SO_4)}$.

(*c*) *Concentration of dissolved* $Fe_2(SO_4)_3$.

(*d*) *Apparent molecular conductivity of* $Fe_2(SO_4)_3$.

in the initial stage. It is obvious that the process occurring in solution during the intermediate equilibrium stage is one of simplification. The solutions formed in the first stage, containing large proportions of the basic ferric ions, are unstable, and break down to form ferric pentaoxysulphate, together with a corresponding quantity of hydrogen ions. The increase in hydrogen-ion concentration displaces the hydrolysis equilibria in solution in the direction of formation of the less basic ions, and the molar conductivity of the iron remaining in solution is thus increased. The specific conductivity of the ferric sulphate (Fig. 8*b*) becomes zero at *E*, where precipitation is complete, and the specific conductivity of the solution (Fig. 8*a*) then rises along the salt line, owing to the formation of sodium sulphate by the

action of sodium hydroxide on the precipitate. This process is complete at F, after which the observed curve is identical with the salt line representing the addition of excess alkali.

The Effect of Excess of Alkali.—The changes in the appearance of the ferric hydroxide precipitate in the region FZ are not accompanied by any change in pH or conductivity, and thus cannot be explained by a reaction between ferric hydroxide and excess of sodium hydroxide. This was confirmed by centrifuging off the precipitate after 5 days, and determining the free sodium hydroxide in the solution. In all cases the quantity found was equal to the calculated excess. By X-ray crystallographic measurements, the precipitate was shown to be goethite, α-$Fe_2O_3.H_2O$. The formation of this compound by the ageing of ferric hydroxide precipitate has been recorded by Krause and Niklewski (*Ber.*, 1938, **71**, 423). The effect of pH upon the rate of formation of this compound, and the complete stability of $Fe(OH)_3$ at pH values less than 8·0, do not appear to have been previously reported.

The Final Equilibrium Stage.—From about 5 days to 6 months after the preparation of the solutions, a gradual change takes place over the whole of the region from just before A, to F, the end of ferric hydroxide formation. Traces of ferric oxypentasulphate appear before A, until after 6 months all those solutions which were characterised by a rise in pH between the initial and intermediate equilbrium states, contain small quantities of this material. Solutions to which less than 9 ml. of sodium hydroxide solution have been added ($SO_3/Fe_2O_3 > 3·2$) remain clear, with no measurable changes in pH or conductivity. The final precipitation curve (Fig. 8*a*, curve 5) is different in type from the intermediate-stage curves. An increase in the quantity of iron precipitated in the early portion of the curve results in the disappearance of the inflexion at C, and its replacement by one at B. The pH curve (Fig. 4) has a maximum just before A, where the pH is little changed from its original value. The existence in this region of a salt less basic than in the rest of the titration is suggested by this observation, while the unchanged appearance of the precipitate, together with the small changes in the pH and conductivities, indicate that the original precipitate of ferric oxypentasulphate remains stable, in the region around A. The height of the pH maximum over the produced portion of the final curve DC is of the order to be expected from the presence of copiapite at A.

In the succeeding portions of the curve, the pH has fallen considerably from the values measured at 48 hours, although the total quantity of the precipitate remains almost unchanged in the region CE. The final pH curve gives no indication of the inflexion at C which characterised the intermediate-stage curves. The fall in pH is accompanied by a change in the appearance of all the precipitates in the region BE, to a uniform drab yellow material, the limits of occurrence of which are in the clearly-defined region BX. The plateau on the pH curve has similarly lengthened, the inflexion at E being replaced by one at X. It is evident that the precipitate of ferric pentaoxysulphate, which existed during the initial and intermediate stages, has hydrolysed further in the solid state, forming a more basic compound, with liberation of sulphuric acid. The composition of this compound is given by the position of X (32·8 ml.), where its formation is complete, and the NaOH : Fe ratio is 8 : 3. This value corresponds with the formation of *ferric octaoxysulphate* [(3 : 1)sulphate], $3Fe_2O_3.SO_3.xH_2O$, which is considered to be the final product of hydrolysis in ferric sulphate solutions in which the $SO_3 : Fe_2O_3$ ratio is between 2·50 and 0·33. A small error in the position of X would lead to a considerable difference in the formula deduced for this compound, but the same value has been found in three series of tests, and is confirmed by conductivity measurements.

Conductivity Changes in the Final Equilibrium Stage.—The final curve of Fig. 6 has been analysed in Fig. 9. The observed curve is very similar to the salt line throughout the titration, the calculated inflexions at A, E, X, and F in the salt line being reproduced exactly by inflexions in the observed curve. Unfortunately, some adsorption of soluble salts has taken place on long standing, with the result that the observed conductivity is below the calculated curve during part of the titration. Consequently, it is not possible to calculate the molar conductivity of the iron remaining in solution. Nevertheless, the conductivity curve is valuable in confirming the deductions made from pH observations. The pronounced conductivity minimum at A confirms the pH maximum observed at this point, and substantiates the presence of ferric oxypentasulphate in this region. The coincidence of the observed curve with the $\kappa_{K_2SO_4}$ curve, which previously occurred at E, now appears at X (32·8 ml.), in confirmation of the pH results, and the rising section EF is correspondingly shortened to XF. These observations give added confirmation of the composition $3Fe_2O_3.SO_3$ for the final compound.

By assuming this composition, it is possible to calculate the composition of the compounds occurring in the region BE during the intermediate equilibrium stage, by a method independent of those previously used. For example, at D:

pH change from 48 hours to 6 months = 2·99—2·34.
Whence, total production of hydrogen ions in 51·6 ml. = $1·82 \times 10^{-4}$ g.-ion.
Total iron precipitated in 48 hours = $7·64 \times 10^{-4}$ g.-atom.
Increase in precipitate from 48 hours to 6 months = $0·27 \times 10^{-4}$ g.-atom.
Production of hydrogen associated with this increase = $0·72 \times 10^{-4}$ g.-ion.
Therefore, quantity of hydrogen ions produced by the hydrolysis of the original precipitate = $(1·82 - 0·72) \times 10^{-4} = 1·10 \times 10^{-4}$.
Calculated H^+ production, assuming the original precipitate to be $Fe_2O_3.2SO_3$, $Fe_2O_3.SO_3$, and $2Fe_2O_3.SO_3$ = $12·7 \times 10^{-4}$, $5·1 \times 10^{-4}$, and $1·27 \times 10^{-4}$ g.-ion, respectively.

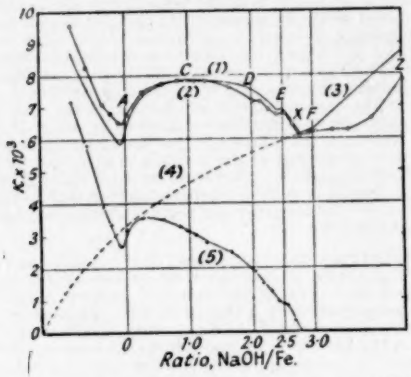
It follows that the original precipitate at D is $2Fe_2O_3.SO_3$, in agreement with previous calculations. Similar results are obtained at other points in the titration.

Reactions in the Presence of Excess of Sodium Hydroxide.—The formation of goethite in the intermediate equilibrium stage is followed by the slow absorption of sodium hydroxide by the precipitate, as

shown by the decreases in the pH and conductivity readings in the region *FZ*. The adsorption of zinc, cobalt, and nickel salts on aged ferric oxides was studied by Kolthoff and Overholzer (*J. Physical Chem.*, 1939, **43**, 767), who considered the effect to be due to the formation of ferrites. It seems very probable that the same process occurs in these experiments. The horizontal portion of the final conductivity curve (Figs. 6 and 9) extends from *F* to about 42 ml. of NaOH, after which the conductivity rises rapidly. Since *F* is at 34·5 ml., the equivalent of 7·5 ml. of 0·1054N-NaOH has been absorbed by the precipitate from 25 ml. of 0·0166M-$Fe_2(SO_4)_3$. Thus 0·95 mol. of NaOH is absorbed by 1 mol. of $Fe(OH)_3$, suggesting the formation of sodium metaferrite, $NaFeO_2$. The slow reactions of hydrated ferric oxide in alkaline solution are the subject of a more detailed study, which will be communicated later.

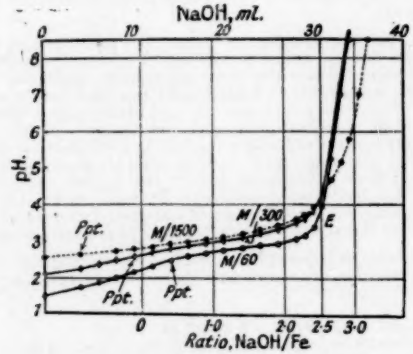
FIG. 9.

Conductivity after 6 months.



(1) $\kappa_{(Na_2SO_4 + H_2SO_4)}$. (2) $\kappa_{(observed)}$. (3) $\kappa_{(NaOH + Na_2SO_4)}$
(4) $\kappa_{Na_2SO_4}$. (5) $\kappa_{H_2SO_4}$.

FIG. 10.



The Effect of Concentration on Titration Results.—The differences which occur in the hydrolysis mechanism of ferric sulphate with increasing dilution suggest that the form of the titration curves should change when the iron concentration is reduced below M/300. Three titrations were carried out, simultaneously, at 25°. In the first, 25 ml. of M/60-feric sulphate solution were titrated with 0·1054N-sodium hydroxide, while in the second and third, the same quantity of solution was diluted to 125 ml. (M/300) and 625 ml. (M/1500) before titration with the same alkali. The point of first precipitation (Fig. 10) becomes progressively earlier at increasing dilution, owing to the increasing effect of hydrolysis. Moreover, while the first two curves are similar in type, the third is markedly different. The general level is little above the second, in spite of the decrease in concentration. If the same three titrations are carried out rather more slowly, the third curve is slightly below the second. This effect is due to the marked increase in the rate of precipitation which occurs in the upper portion of the pH–dilution curve

(Fig 2), and suggests that at low concentrations the condition which has been called the "initial equilibrium stage" is of only momentary duration. It is noticeable that the precipitate formed in the region *AE*, at M/1500-concentration, is a yellow powder resembling the product of the intermediate equilibrium stage, rather than the gelatinous compound initially formed in M/60-solutions. The inflexion observed at *E* in curves 1 and 2 is almost indiscernible in curve 3, showing that the transformation of the basic salt into the hydroxide is a much less clearly-defined process at lower concentrations.

Discussion.

The Basic Sulphates.—The evidence of this work indicates the formation, according to the conditions, of three basic sulphates: ferric oxypentasulphate, $2Fe_2O_3,5SO_3,xH_2O$, corresponding to the mineral copiapite; ferric pentaoxysulphate, $2Fe_2O_3,SO_3,xH_2O$, equivalent to the minerals glockerite and hydroglockerite; and ferric octaoxysulphate, $3Fe_2O_3,SO_3,xH_2O$, which has not previously been reported. The postulation of the ions $FeOH^{++}$ and $Fe(OH)_2^+$ suggests that the corresponding basic sulphates $2Fe_2O_3,SO_3$ and Fe_2O_3,SO_3 may occur as intermediate stages in the hydrolysis and titration processes. It is known that ferric oxydisulphate, $Fe_2O_3,2SO_3$, occurs as a series of minerals in various states of hydration between those of butlerite ($2H_2O$) and fibroferrite ($10H_2O$). Similarly, ferric dioxysulphate [(1 : 1)sulphate], Fe_2O_3,SO_3, exists as borgstromite (anhydrous) and planoferrite ($15H_2O$), together with intermediate compounds. Posnjak and Merwin (*J. Amer. Chem. Soc.*, 1922, **44**, 1983), in phase-rule studies at 75—200°, showed that $Fe_2O_3,2SO_3$ occurred as a solid phase at all temperatures, the hydration varying according to the temperature. The results of this work do not indicate the presence of either ferric dioxysulphate or ferric oxydisulphate for any finite period of time at 25°. One observation exists, however, to suggest their momentary formation during the initial equilibrium stage. It has been shown that in the intermediate equilibrium stage, ferric pentaoxysulphate occurs in three forms which can be distinguished visually, the boundaries between them coinciding with inflexions in pH and conductivity curves at *C* and *D*. Since the state of the solution at the intermediate stage is little changed throughout the titration, the difference in the form of the precipitate must result from some difference in the mechanism of precipitation in the regions *AC*, *CD*, and *DE*. A possible process would be the initial formation of $Fe(OH)SO_4$, $[Fe(OH)_2]_2SO_4$, and $[Fe_2(OH)_4]_2SO_4$ in these regions, followed immediately by their conversion into three forms of $[Fe_2(OH)_4]_2SO_4$, which lose water during the second equilibrium stage, to give three different hydrates of $2Fe_2O_3,SO_3$.

Basic Ions.—The hydrolysis of ferric sulphate solutions can be explained quantitatively by the postulation of the ions Fe^{+++}, $FeOH^{++}$, and $Fe(OH)_2^+$ as the only ones present in solution. The presence of FeO^+ ions in solutions obtained from the ultra-filtration of ferric hydroxide sols has been demonstrated by Krestinskaya and Khavimov (*J. Gen. Chem. U.S.S.R.*, 1944, **14**, 70), and evidence for the existence of $FeOH^{++}$ has been given by the absorption-spectra studies of Rabinowitch and Stockmeyer (*loc. cit.*). The formation of ferric oxypentasulphate and ferric pentaoxysulphate, which can be considered as the sulphates of Fe_2OH^{5+} and $Fe_2(OH)_4^+$, suggests the possibility that the hydrolysis process may occur through the medium of diatomic ions. In this case, equilibria would occur between Fe^{3+}, Fe_2^{6+}, Fe_2OH^{5+}, $Fe_2(OH)_2^{4+}$, $Fe_2(OH)_4^{2+}$, and $Fe_2(OH)_3^+$. No evidence has been found for an ion of the type $Fe_2(OH)_2^{3+}$. The postulation of the diatomic process involves some difficulties, since the increase in pH in the region *AB* during the intermediate equilibrium stage is less easy to explain if the ion Fe_2OH^{5+} is considered to be present from the beginning. The monatomic hydrolysis process is preferred, as giving the simplest mechanism reconcilable with all observations.

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Chemical Research Laboratory, Teddington, Middlesex. [*Received, July 27th*, 1950.]

79. *Structure of an Antigenic Polysaccharide Isolated from Tuberculin.*

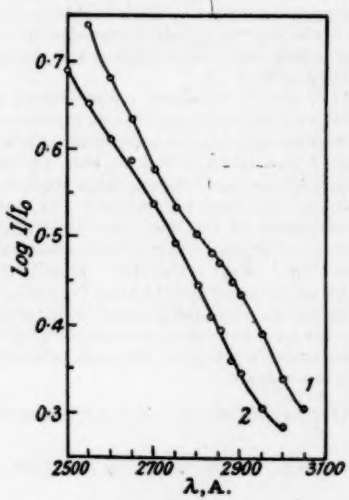
By P. W. Kent.

A substance which had been isolated from the human-type *M. tuberculosis* (strain H37.A33) and which, in a previous communication, was reported to be electrophoretically homogeneous and capable of eliciting antibodies, has been found to consist of a polysaccharide component (92%) and a lipoid component (8%). The polysaccharide component contained nitrogen and gave positive tests for a 2-amino-sugar. Chromatographic analysis of the hydrolyzed material showed that the principal monosaccharide constituent was glucose and that glucosamine was present. The polysaccharide component was investigated by the methylation technique. The products of hydrolysis of the methylated derivative consisted almost entirely of 3 : 4 : 6-trimethyl glucose. The polysaccharide therefore consists mainly of glucopyranose units linked in the 1 : 2-positions. The molecular weight of the native substance measured by a light-scattering technique was of the order $4{\cdot}9 \times 10^5$ (cf. 1×10^5 obtained previously from ultra-centrifuge investigations).

It has been shown (Seibert, Stacey, and Kent, *Biochem. Biophys. Acta*, 1949, **3**, 632) that an antigenic polysaccharide can be isolated from culture filtrates of certain types of *M. tuberculosis*. This polysaccharide (designated polysaccharide II in order to differentiate it from the non-antigenic polysaccharide I also present in tuberculin-bearing filtrates) contained nitrogen—a finding consistent with detection of an amino-sugar component in the material. The preliminary examination, whilst it revealed the presence of glucose as the major monosaccharide component, also indicated the presence of some non-reducing constituent, and this was further substantiated by the slight amount of specific absorption in the ultra-violet region (2800—2880 A.). The absorption band disappeared (Fig. 1) when a solution of the native substance was treated with benzene at pH 11 at 80°. The polysaccharide was recovered from the aqueous solution by precipitation with alcohol after acidification (it was then purified by dissolution in water, dialysis, and reprecipitation). The benzene layer was dried and the solvent distilled off, yielding a small amount of lipoid material which appeared to be a mixture of fatty acids and corresponded to 8% of the original material. The quantity obtained was too small for further study.

Fig. 1.

Ultra-violet absorption spectra.



(1) Native, (2) lipoid-free polysaccharide.

The specific rotation of the original polysaccharide II was +160° (*c*, 0·25 in water) and after defatting was +183·5° (*c*, 0·22 in water). The amount of reducing sugar, measured by the Shaffer–Hartmann technique (*J. Biol. Chem.*, 1921, **47**, 477), also increased from 84% to 94·1%. The serological activity of the native and the defatted material was studied by Dr. F. B. Seibert of the Henry Phipps Institute by means of the precipitin reactions, antitubercle bacilli horse serum (A5807) being used, and both were found to react in dilutions of 1 : 200,000 (see Table I). The properties of the substances are summarised in Table I.

It seems therefore that the substance is a lipo-polysaccharide containing 1 part of lipoid to 11 parts of polysaccharide, moving as an entity on electrophoresis but dissociated in aqueous alkali at slightly elevated temperatures, and that the lipoid constituent is not apparently involved in the reaction with homologous serum in the precipitin test. The native material

was readily hydrolyzed by acid and in this respect differed from Anderson's fatty acid–polysaccharide waxes (*Chem. Reviews*, 1941, **29**, 225). The equilibrium value, $[\alpha]_D$ +52°, was reached after 2 hours' heating with N-acid. In the sugars so produced only glucose could be

TABLE I.

Comparison of native and lipoid-free polysaccharide.

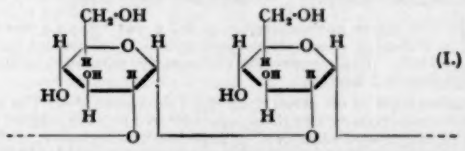
	Native.	Defatted.
$[\alpha]_D$ in water	+160°	+183·5°
Log I/I_0 at 2830 A. (c = 0·25% in water)	0·480	0·410
Reducing sugar, % (max. value)	84·2	94·1
Precipitin titre	1 : 200,000	1 : 200,000

detected, but there was a positive test for amino-sugar. Glucose had been identified earlier both as the anilide and as the diethyl mercaptal penta-acetate.

Paper-chromatographic examination of the hydrolyzed polysaccharide (Partridge, *Nature*, 1946, **158**, 270; *Biochem. J.*, 1948, **42**, 238) showed that one principal reducing sugar was present, namely glucose. A second weakly-reducing band was detected, corresponding to glucosamine both in its reduction of silver nitrate and in its colour with ninhydrin. The presence of glucosamine was confirmed by the formation of the *N*-(2 : 4-dinitrophenyl) derivative by treatment of the hydrolyzed polysaccharide with 1-fluoro-2 : 4-dinitrobenzene and sodium hydrogen carbonate. Chromatographic examination of the product showed that only dinitrophenylglucosamine and glucose were present (Kent, *Research*, 1950, **3**, 427). There was no evidence of the presence of amino-acids (Kent, Lawson, and Senior, *Science*, 1950, in the press).

The mixture of glucosides formed by methanolysis of the methylated polysaccharide had OMe 53·2% (a trimethyl methylhexoside requires 52·54%) and this was taken as indicating that the fraction consisted mainly of a trimethyl methylglucoside. Paper-chromatographic examination of the hydrolyzed mixed glycosides (Brown, Hirst, Hough, Jones, and Wadman, *Nature*, 1948, **161**, 720) showed the presence of only one principal band and this corresponded to 3 : 4 : 6-trimethyl glucose. The absence of any significant quantity of di- or tetra-methyl sugar suggests either a long-chain structure with little branching (which is in agreement with the sedimentation and diffusion investigation of the material) or a closed-chain structure. The trimethyl methylglucoside (*A*) (n_D^{18} 1·4640) was almost entirely soluble in light petroleum but there remained a small amount of insoluble material (*B*) (n_D^{18} 1·4660), the quantity of which did not permit further investigation. The glucoside *A* was hydrolysed with dilute mineral acid, to yield a syrupy free-sugar derivative. This free sugar did not yield a crystalline anilide but with phenylhydrazine in acid solution yielded 3 : 4 : 6-trimethyl glucosazone; it was oxidized by bromine water to the corresponding acid. Distillation of the acid in a high vacuum gave a non-crystalline lactone (OMe 42·6%) which afforded a good yield of crystalline 3 : 4 : 6-trimethyl D-gluconophenylhydrazide. The corresponding non-crystalline amide gave a positive Weerman test indicative of an α-hydroxy-group.

This evidence indicates that in the polysaccharide moiety a large part of the glucose residues are linked through the 1 and the 2 position and are in the pyranose form [as (I)]. The failure to detect any dimethyl methylhexoside in the hydrolyzate of the methylated polysaccharide suggests that the polysaccharide may have little branched-chain structure. The slow rate of oxidation of the polysaccharide by potassium periodate, under controlled conditions, precludes the possibility of a wholly dextran-like structure (Kent, *Science*, 1949, **110**, 689).



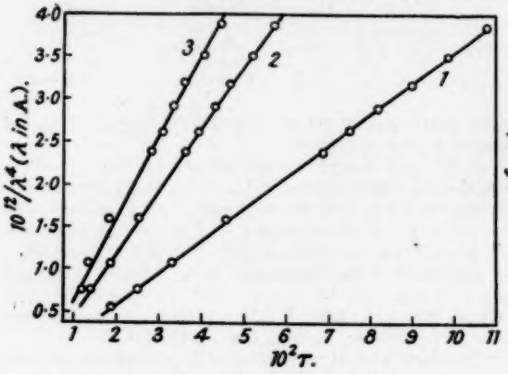
(I.)

The molecular weight of the native material calculated from diffusion constant–sedimentation data was of the order of 1×10^8. In dilute aqueous solution, the material exhibited the common Tyndall blue colour. In a preliminary examination of such solution by the light-scattering technique (Debye, *J. Appl. Physics*, 1944, **15**, 338; *J. Physical Chem.*, 1947, **51**, 18; Ostler, *Chem. Reviews*, 1948, **43**, 319; Mark, "Chemical Architecture," Interscience, 1948, p. 121) it was found that the turbidity (from λ 4000 to 6000 A., measured on a Beckman absorption spectro-

meter) was accurately proportional to λ^{-4}. (Fig. 2). The molecular weight obtained from the measurements was $4{\cdot}9 \times 10^5$ (Fig. 3). This value is only approximate as backward and

FIG. 2.

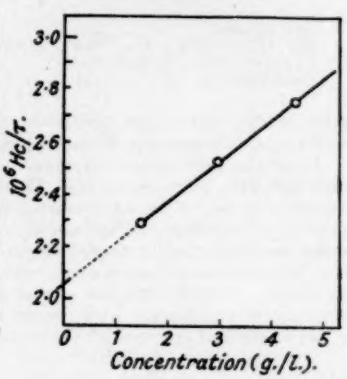
Relation between turbidity (τ) and $1/\lambda^4$ at various concentrations.



Concentrations: 1, 4·430 *mg./c.c.*; 2, 2·960 *mg./c.c.*; 3, 1·48 *mg./c.c.*

FIG. 3.

Extrapolation of the turbidity relation against concentration.



forward scattering factors were not taken into account, but it is significant as it is of the same order as the value deduced from ultra-centrifuge determinations.

EXPERIMENTAL.

The native substance gave negative results in the Bial test for pentoses and in Tollens's reaction. The Molisch test was positive (+++), and the test (after preliminary acidic hydrolysis) for amino-sugars was positive (+) (Elson and Morgan, *Biochem. J.*, 1933, **27**, 1824). The substance had $[\alpha]_D^{19}$ +160° (*c*, 0·25 in water).

Action of Dilute Alkali and Benzene.—The native substance (0·394 g.) was dissolved in 0·001N-sodium hydroxide (20 c.c.) to which was added benzene (10 c.c.), and the mixture was heated at 80° under reflux for 20 hours. The solution was made acid (pH 5) with dilute acetic acid. The aqueous layer was dialysed against distilled water for 3 days and the defatted polysaccharide precipitated by addition of alcohol (5 vols.). The moist product was dissolved in water (10 c.c.) and dried by lyophylization, and finally over phosphoric oxide (yield, 0·352 g.).

The benzene layer was dried (K_2CO_3) and evaporated in a weighed flask. The resulting lipoidal non-crystalline solid (0·031 g.) was not soluble in water. A specimen of the native substance was hydrolyzed in the absence of benzene; after 1 hour a white flocculent precipitate separated.

The defatted polysaccharide had $[\alpha]_D^{19}$ +183·5° (*c*, 0·22 in water). An aqueous solution (0·25%), examined in the Beckman photospectrometer, showed only general absorption between 2500 and 3000 A. (E at 2800 A. = 0·480).

Absorption Spectra of the Native Polysaccharide.—An aqueous solution (0·25%) showed a small but distinct absorption between 2800 and 2870 A., E at 2830 A. being 0·480.

Acid Hydrolysis.—(i) The native polysaccharide (*c*, 0·2 g. per 100 c.c.) was hydrolyzed at 100° with 0·1N-sulphuric acid; the following observations were made: $[\alpha]_D^{19}$, initial, +165°; after 30 minutes, +183°; after 9 hours, +140°. (ii) On hydrolysis of the native substance with N-sulphuric acid at 100°, $[\alpha]_D^{20}$ fell to +52° (equilibrium in 2 hours).

Chromatographic Examination of the Monosaccharide Constituents.—(i) The acid-hydrolyzate (above) was neutralized with barium carbonate, and the solution filtered and evaporated to dryness. The residue was taken up in water (2 drops) and submitted to paper chromatography, with butanol–water–ethanol (40 : 50 : 10) as eluant. One main band (R_F, 0·18) was observed, corresponding to that given by glucose (0·18) when examined simultaneously. The band was detected by means of aniline hydrogen phthalate.

A second band (R_F 0·1) was observed by treatment of the paper with silver nitrate. The same band gave a blue colour with ninhydrin and was therefore thought to be an amino-sugar (R_F for glucosamine, 0·08). (ii) The initial polysaccharide (15 mg.) was hydrolyzed in a sealed tube with N-sulphuric acid (1 c.c.) at 110° for 3 hours. The hydrolysate was neutralised with sodium hydrogen carbonate (0·05 g. excess), and the resulting solution was shaken with 1-fluoro-2 : 4-dinitrobenzene (3 drops) for 2 hours. Three drops of the reaction mixture were applied to the paper chromatogram which was eluted with the

above-mentioned mixture. A yellow band (R_F 0·74) was observed which corresponded to authentic *N*-2 : 4-dinitrophenylglucosamine (m. p. 167—169°; R_F 0·75) when investigated simultaneously on the same paper chromatogram. When the paper was sprayed with a solution of aniline hydrogen phthalate and warmed, the yellow band became brown (a characteristic of dinitrophenylamino-sugars) and another band corresponding to glucose appeared.

Action of Amylase.—The native polysaccharide (17 mg.) was incubated at 25° and at 35° with β-amylase obtained from soya bean by Dr. E. J. Bourne. There was no liberation of reducing sugar as measured by the Shaffer–Hartmann method.

Reducing-sugar Content.—(*a*) Native polysaccharide (2·50 mg.) was hydrolyzed with N-sulphuric acid (1 c.c.) for 4 hours at 100°, then neutralized with sodium carbonate, and the reducing sugar in the resulting solution was determined (Shaffer–Hartmann) : 2·34 mg. of glucose were found. The reducing sugar content calculated as glucose was 84·2% (constant value).

(*b*) Defatted polysaccharide (1·08 mg.) was hydrolyzed, neutralized, and titrated with Shaffer–Hartmann reagent, 1·13 mg. of glucose were found, equivalent to 94·1% calculated as glucose.

Methylation.—(*a*) The native polysaccharide (0·1 g.) was methylated by means of liquid ammonia (5 c.c.), sodium (0·2 g.), and methyl iodide (1 c.c.) since it could be demonstrated that under the action of liquid ammonia alone, the viscosity of the polysaccharide in water was not appreciably changed. The methylated product, however, was not wholly insoluble in the liquid ammonia and this method was abandoned in favour of the Haworth method.

(*b*) A typical methylation was carried out on 0·3 g. of the native polysaccharide by the use of 5N-sodium hydroxide (3 c.c.) and methyl sulphate (1 c.c.), added dropwise during 1 hour, the mixture being kept slightly alkaline throughout. The mixture was stirred for a further hour, and excess of methyl sulphate destroyed by heating the mixture rapidly to 90°. The liquid was neutralized by sulphuric acid, and the partly methylated derivative which separated was collected. After two such methylations the derivative was soluble in chloroform, and after four methylations the product was treated with methyl iodide and dry silver oxide, until the methoxyl content became constant (44·4%); 0·2 g. of product was obtained, which had been freed from gross impurities by precipitation with light petroleum.

Hydrolysis of the Methylated Polysaccharide.—The methylated polysaccharide (0·38 g.) was hydrolyzed by boiling methanolic hydrogen chloride (5 c.c.; 0·1 N.); $[\alpha]_D$ (originally +144°) became +107° in 10·5 hours (not constant). N-Methanolic hydrogen chloride caused $[\alpha]_D$ to fall to +66° (constant) in 2 hours. The solution was neutralized by silver carbonate and filtered and the solution treated with a small volume of light petroleum to precipitate suspended silver salts. After filtration, the solution was gently dried under a slightly reduced pressure, yielding a syrup (0·30 g.), $[\alpha]_D$ +68° (in methanol), n_D^{18} 1·4645 (Found : OMe 53·2%).

Examination of the Methylated Fraction.—(*a*) The methylated sugar (0·03 g.) was hydrolyzed by hot 0·5N-hydrochloric acid (2 c.c.) for 4 hours, neutralized (silver carbonate), filtered, and concentrated almost to dryness. Paper chromatography as above gave only one band (R_F 0·76) on a Whatman No. 1 filter paper (R_F for 3 : 4 : 6 trimethyl glucose, 0·74 under the same conditions).

(*b*) The partly methylated sugar (0·2 g.) was extracted several times with dry light petroleum. The solution yielded, on evaporation, 0·17 g. of material (*A*), n_D^{18} 1·4440, and 0·01 g. of a residue (*B*), n_D^{18} 1·4660.

Isolation of 3 : 4 : 6-*Trimethyl* D-*Glucosazone.*—A portion of the fraction *A* (0·1 g.) was hydrolyzed with 0·1N-sulphuric acid (7 c.c.) {$[\alpha]_D$ +49° ⟶ +42° (8 hours)}. There was no further change when the concentration of acid was increased to N. The solution was neutralized (phenolphthalein) with aqueous sodium hydroxide, evaporated to dryness, and extracted with chloroform. Evaporation of the solvent yielded a syrup (0·08 g.) which on chromatography showed only one band (R_F 0·76) (R_F found for 3 : 4 : 6-trimethyl glucose, 0·74). Of this reducing syrup 30 mg. were refluxed with aniline (15 mg.) in dry ethanol (2 c.c.) for 3 hours, but no crystalline anilide was obtained. A further 40 mg., in acetic acid (1 c.c.; 1N.), were heated with phenylhydrazine hydrochloride (25 mg.) at 90° for 45 minutes and the orange solid which formed was filtered off and crystallized from a little alcohol; it had m. p. 78—80° alone or on admixture with authentic 3 : 4 : 6-trimethyl glucosazone (Haworth, Hirst, and Isherwood, *J.*, 1937, 782).

Identification of 3 : 4 : 6-*Trimethyl Gluconohydrazide.*—The partly methylated free sugar (0·35 g.) obtained by aqueous acidic hydrolysis of either the methylated polysaccharide or the products of methanolysis was dissolved in water (10 c.c.), and bromine (0·5 c.c.) added. The solution was kept at room temperature until it ceased to reduce Fehling's solution (3 days). The excess of bromine was removed by aeration, and the acid neutralized with silver carbonate. The filtrate was saturated with hydrogen sulphide, filtered, and evaporated to dryness. The product was extracted with chloroform and then distilled [b. p. 115—119° (bath-temp.)/0·05 mm.] and had n_D 1·4640 (0·26 g.) (Found : OMe, 42·6. Calc. for trimethyl gluconolactone : OMe, 41·5%). The lactone so obtained did not crystallize but with the calculated amount of phenylhydrazine at 100° for 20 minutes in water gave a crystalline product which, recrystallized from ethyl acetate, had m. p. 124—125° (Found : OMe, 28·2%) [3 : 4 : 6-trimethyl gluconophenylhydrazide (Haworth and Pannizon, *J.*, 1934, 154) (OMe, 28·5%) has m. p. 126°]. The lactone was treated with saturated methanolic ammonia at 0° for 4 hours. A syrup resulted with sodium hypochlorite at 0° and gave a product which with saturated semicarbazide hydrochloride yielded a hydrazodicarbonamide (Weerman, *Rec. Trav. chim.*, 1917, **36**, 16), m. p. 252—253°.

Molecular Weight by Light Scattering.—A solution of the dry dialyzed native material in water (4·43 mg./c.c.) was passed twice through a fine sintered-glass filter. From this two dilutions were made, giving solution containing 1·48 and 2·96 mg./c.c. respectively.

The linear relationship between turbidity (τ) and $1/\lambda^4$ was demonstrated for all three solutions examined in the range 6000—4000 A (Fig. 2). Results for 5000 A. and 21·1° are given in the following table. Fig. 3 is drawn from these results. If $H = 32\pi^3\mu^2(\text{solvent}).\Delta\mu^2/3N\lambda^4c^2$, where N = Avogadro's number, c = concentration, $\Delta\mu = \mu(\text{solution}) - \mu(\text{solvent})$, λ = wave-length in cm., and μ(solvent) was found to be 1·33327, then the following equation holds: $Hc/\tau = 1/M + 2Bc$ . . ., where τ = turbidity, M = molecular weight, and B is a coefficient.

$10^3 \times$ Concn. (c) (g./c.c.).	μ(solution).	$10^3\,\Delta\mu$.	τ.	$10^6\,Hc/\tau$.
4·43	1·33596	2·69	0·092	2·76
1·48	1·33417	0·900	0·037	2·27
2·96	1·33507	1·8	0·051	2·53

In Fig. 3, Hc/τ was plotted against c. Extrapolation to zero concentration gave an intercept value for $1/M = 2{\cdot}05 \times 10^{-6}$, whence the molecular weight = $4{\cdot}9 \times 10^5$.

The author thanks Dr. F. B. Seibert of the Henry Phipps Institute, Philadelphia, for her gift of material and for her generous advice and co-operation, the University of Princeton, New Jersey, for the award of a Rockefeller Foundation Fellowship, and Professors Hugh S. Taylor and Eugene Pacsu for their interest.

FRICK CHEMICAL LABORATORIES, PRINCETON UNIVERSITY,
NEW JERSEY. [*Received, August 8th*, 1950.]

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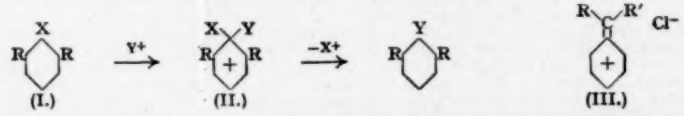
80. *The Effect of Intramolecular Configuration on the Rate of Unimolecular Solvolysis of Aralkyl Chlorides.*

By G. BADDELEY and J. CHADWICK.

3-Hydroxy- and 3-chloro-1 : 2-benz*cyclo*heptene have been prepared. The rates of ethanolysis of 1-phenyl-, 1-*o*-tolyl- and 1-mesityl-ethyl chlorides and of 1-chloroindane, 1-chlorotetralin, and 3-chloro-1 : 2-benz*cyclo*heptene have been measured at two temperatures; in general, increased reactivity is caused by diminution in activation energy. The high reactivity of 1-chloroindane and 1-chlorotetralin is related to the essentially planar structure of the respective carbon skeletons. It is argued that ionisation of the other chlorides is accompanied by intramolecular reorientation and that this is subject to steric hindrance.

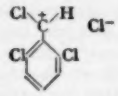
ONE of us pointed out (*Nature*, 1939, **144**, 444; 1942, **150**, 178) that, whereas some reactions are sterically hindered, others are sterically facilitated. In the latter, steric interaction in the transition state is less than that in the reactant. The naïve assumption that bimolecular reactions are of the former type while unimolecular ionisation processes are of the latter is to be avoided. There are many instances in which the bimolecular replacement of a bulky group X in a benzene derivative (I) is possible only when bulky *ortho*-substituents are present, and it has been suggested (*loc. cit.*) that this arises from the decrease in steric interaction in passing from (I) to the transition state (II). On the other hand, we now show that the ionisation of an aralkyl chloride, $\text{Ar·CRR'Cl} \longrightarrow \text{Ar·}\overset{+}{\text{C}}\text{RR'} + \text{Cl}^-$, is subject to steric hindrance.



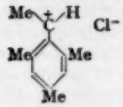
(I.) (II.) (III.)

The ionisation process, which is the rate-determining step in the unimolecular solvolysis of alkyl and aralkyl halides, entails a tetrahedral carbon atom becoming a planar carbonium ion (Hughes, Ingold, *et al.*, numerous papers since 1935) and provides an intramolecular reorientation of the carbon skeleton which alters the magnitude of intramolecular steric interaction. Thus unimolecular solvolysis is subject to steric effects which arise solely from this change in the configuration of the carbon skeleton. For example, solvolysis of a *tert.*-alkyl halide is facilitated sterically by the decrease in the energy of steric interaction between alkyl groups which accompanies the process $\text{RR'R''CCl} \longrightarrow \text{RR'R''C}^+ + \text{Cl}^-$, the alkyl groups

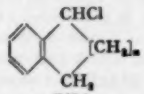
being more widely separated in the cation than in the chloride. Ionisation of an aralkyl chloride Ar·CRR′Cl, however, is subject to more stringent steric requirements; it is facilitated by conjugation between the side-chain and the benzene ring in the cation $Ar\cdot\overset{+}{C}RR'$, and this activating effect of the aryl group, on the basis of resonance with quinonoid structures like (III), is fully operative only when the cation is planar. The formation of such structures is known to be obstructed by one bulky *ortho*-substituent when both R and R′ (of III) are large atoms or groups and by two bulky *ortho*-substituents when R only is large; thus the steric inhibition of resonance which was first recognised more than ten years ago (Hampson *et al.*, *J.*, 1937, 10; 1939, 981; Baddeley, *loc. cit.*) and is one of several causes of " *ortho*-effects " (Hughes, *Quart. Reviews*, 1948, **2**, 107), can be a feature of the unimolecular solvolysis of a benzyl halide. This argument is difficult to substantiate as the introduction of bulky *ortho*-substituents provides additional inductomeric and possibly electromeric effects which are hard to disentangle from steric effects. For example, the low reactivity of 2 : 6-dichlorobenzylidene chloride in 50% aqueous acetone (Loch and Asinger, *Monatsh.*, 1932, **59**, 152, record 2 : 6-dichloro- ≪ 2-chloro-benzylidene chloride < benzylidene chloride) is due, at least in part, to the inductive effect of the chlorine atoms attached directly to the benzene ring, and cannot be assigned to the steric inhibition of resonance in the cation (IV). Again, we have now observed that 1-mesitylethyl chloride, no doubt as a consequence of the inductive effect of its methyl groups, reacts rapidly with ethanol (Table I), despite the probable steric inhibition of resonance in the cation (V).



(IV.)



(V.)



(VI.)

The absorption spectrum of 1-methyl-2 : 3-benz-1-aza*cyclo*hept-2-ene and its low reactivity in the hydrogen-exchange reaction are both quoted as evidence that the conformation of the seven-membered ring partly inhibits conjugation between the nitrogen atom and the benzene ring (Remington, *J. Amer. Chem. Soc.*, 1945, **67**, 1838; Brown, Widiger, and Letang, *ibid.*, 1939, **61**, 2597), and we recognised that a comparison of 3-chloro-1 : 2-benz*cyclo*heptene (VI; $n = 3$) with 1-chlorotetralin (VI; $n = 2$), 1-chloroindane (VI; $n = 1$) and 1-*o*-tolylethyl chloride would demonstrate unambiguously, the uncertainties arising from the introduction of additional *ortho*-substituents being avoided, the effect of intramolecular configuration on the rate of unimolecular solvolysis of benzyl chloride derivatives.

Benzosuberone was obtained in good yield (*ca.* 80%) by the interaction of δ-phenyl-*n*-valeryl chloride and aluminium chloride in ethylene chloride; lower yields were obtained in light petroleum (Kipping and Hunter, *J.*, 1901, 602) or carbon disulphide (Borsche and Roth, *Ber.*, 1921, **54**, 174). Benzosuberol was readily obtained by reduction of this with aluminium

TABLE I.

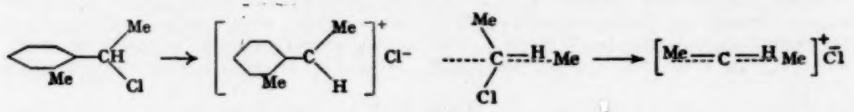
Constants of Arrhenius equation, $k = Ae^{-E/RT}$, for the formation of hydrogen chloride by the ethanolysis of the chlorides.

	$10^7 k_{0.0}$ (mins.$^{-1}$).	$10^5 k_{25.0}$ (mins.$^{-1}$).	E, kcals./mole.	$10^{-15}A$ (secs.$^{-1}$).
1-Mesitylethyl chloride	6800	1960	21·9	290
1-Chloroindane	4000	870	20·0	5·9
1-Chlorotetralin	1070	239	20·2	2·1
1-*o*-Tolylethyl chloride	66	22·0	22·8	15
3-Chloro-1 : 2-benz*cyclo*heptene	23·5	9·2	23·9	38
1-Phenylethyl chloride	1·94	0·99	25·6	93

*iso*propoxide and, like 1-phenylethyl alcohol, was readily converted into the corresponding chloride by thionyl chloride in the presence of pyridine. This procedure was unsatisfactory for the preparation of the readily hydrolysed 1-chloroindane and 1-chlorotetralin, and these were obtained by the addition of hydrogen chloride to indene and 1 : 2-dihydronaphthalene respectively. Their times of half-reaction in 50% aqueous acetone at 17° are 3—10 seconds. Unimolecular solvolysis occurs less readily in solvents of lower dielectric constant (Hughes, Ingold, *et al.*, *loc. cit.*), and the data in Table I were obtained in absolute ethanol. The rates of hydrogen chloride formation were measured conductometrically.

These reactions, like that of 1-phenylethyl chloride (Ward, *J.*, 1927, 445; Hughes, Ingold, and Scott, *J.*, 1937, 1201), are unimolecular, their rates being unaffected by small additions of sodium ethoxide. When these chlorides were added to very dilute ethanolic sodium ethoxide, the conductivity remained constant while sodium ethoxide was present and then rose sharply as the solution became acidic. Greater concentrations of sodium ethoxide provided a conductivity which was constant at first but subsequently fell gradually, owing to precipitation of sodium chloride, and passed through a sharp minimum as the mixture became acidic. The rates of reaction, obtained by measuring the times required for the neutralisation of known quantities of sodium ethoxide, were in good agreement with those obtained in the absence of ethoxide ions.

The results in Table I show that, in general, increased reactivity is caused by a diminution in activation energy (E) and that the action constant (A) varies so as to compensate partly for the change in E; such compensation effects have been discussed by Hinshelwood (" Kinetics of Chemical Change," Oxford, 1940, p. 257) and Christiansen (*Acta Chem. Scand.*, 1949, **3**, 61). The relative rates of ethanolysis, 1-chloroindane > 1-chlorotetralin ≫ 3-chloro-1 : 2-benz*cyclo*heptene, are strikingly similar to the relative rates of hydrogen exchange, 1-methylindoline > 1-methyltetrahydroquinoline ≫ 1-methyl-2 : 3-benz-1-aza*cyclo*heptene, observed by Brown, Widiger, and Letang (*loc. cit.*), and can be explained in terms of partial steric inhibition of resonance by a puckered seven-membered ring. When 1-*o*-tolylethyl chloride is included in the comparison, however, the outstanding feature is the high reactivity of 1-chloroindane and 1-chlorotetralin. The carbon skeletons of these two chlorides have essentially the same planar configuration as is required for maximum resonance energy in the corresponding cations; this does not apply to 3-chloro-1 : 2-benz*cyclo*heptene or 1-*o*-tolylethyl chloride, and the additional energy needed to ionise them can arise because (i) ionisation is accompanied by intramolecular reorientation in which non-bonded atoms or groups are brought closer together so that their energies of interaction consequently increase (ii) steric interaction provides a non-planar cation of comparatively low resonance energy. The latter circumstance arises when deviation from planarity effects a diminution in steric interaction which more than compensates for the loss in resonance energy. It is plausible to assume that this does not obtain in the 1-*o*-tolylethyl cation, and the manner in which steric interaction may hinder the ionisation of 1-*o*-tolyl ethyl chloride is illustrated below. The formulæ on the right, in which the broken line represents the benzene ring, are projections on a plane perpendicular to the Ar–CHMeCl bond. If the chloride is given the configuration in which steric interaction is a minimum, the methyl group of the side-chain being well separated from the *ortho*-positions, then, as resonance ensures the planarity of the cation, *ionisation of the chloride is hindered by the energy needed to bring the methyl group into the plane of the benzene ring.* This incursion of steric interaction is not in doubt.

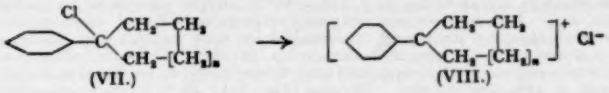


I

The distance separating the side-chain methyl group from the *ortho*-position in the cation is comparable with that separating (i) the *o*- and the *o'*-position in diphenyl or (ii) the methyl groups in *cis*-but-2-ene. The concomitant steric interactions in these substances are reflected respectively by the non-planar structure of diphenyl in the liquid and the gaseous state (Bastiansen, *Acta Chem. Scand.*, 1949, **3**, 408) and by the difference of *ca.* 1 kcal./g.-mol. between the *cis*- and the *trans*-form of but-2-ene (Kistiakowsky *et al.*, *J.*, *Amer. Chem. Soc.*, 1935, **57**, 876).

Although the comparatively slow ethanolysis of 3-chloro-1 : 2-benz*cyclo*heptene may, on the above argument, be derived from the energy which is needed to bring the α-methylene group into the plane of the benzene ring, there is also the possibility that it is caused by partial inhibition of resonance in the cation obtained when this chloride is ionised. There is no definite evidence to support the latter possibility. The rates of interaction of semicarbazide with indan-1-one, 1-tetralone, and benzosuberone, ultra-violet absorption data for these ketones and for their oximes and semicarbazones, the Raman frequencies for the carbonyl group in these ketones, and ultra-violet absorption data for indene, 1 : 2-dihydronaphthalene, and 1 : 2-benz*cyclo*hepta-1 : 3-diene are assembled in the Experimental section; they provide on definite evidence that those substances containing a seven-membered ring are subject to steric hindrance of resonance.

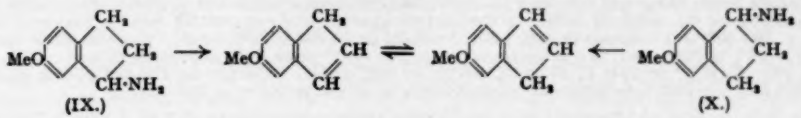
These steric considerations lead to the view that the ionisation of a tertiary aralkyl halide Ar·CRR′X, in contrast with that of a *tert.*-alkyl halide, is sterically hindered, energy being needed to bring the alkyl groups R and R′ into the plane of the ring. This view can account for our observation (details will be communicated later when the rates of unimolecular solvolysis



(VII.) (VIII.)

of *cyclo*pentyl and *cyclo*hexyl chloride are available for comparison) that the rate of unimolecular ethanolysis of 1-phenyl*cyclo*pentyl chloride (VII; $n = 1$) is many times faster than that of the corresponding *cyclo*hexyl chloride (VII; $n = 2$); in fact, this difference in rate was expected since, in the cation (VIII; $n = 1$) the *cyclo*pentyl group holds the α-methylene groups away from the *ortho*-positions of the benzene ring and so effects a diminution in steric interaction. This effect of the five-membered ring has been substantiated in other instances; the comparatively stable complex of tetrahydrofuran with boron trifluoride (Brown and Adams, *J. Amer. Chem. Soc.*, 1942, **64**, 2557) and the greater stability of pyrrolidine–trimethylboron compared with piperidine–trimethylboron (Brown and Gernstein, *ibid.*, 1950, **72**, 2926) have been attributed to the reduced steric effect of the α-methylene groups of a five-membered ring.

The comparatively high reactivity of reactants which have the same configuration, usually planar, as is required for maximum resonance energy in the transition state, *e.g.*, that of 1-chloroindane and 1-chlorotetralin, is further illustrated by the hydrochlorides of the amino-



(IX.) (X.)

indanes (IX) and (X) which form ammonium chloride " with quite remarkable ease " (Ingold and Piggott, *J.*, 1923, 1472). These authors made the further significant observation that unlike 1 : 3-diphenylpropene, " which is definitely static, indene is mobile, being strictly comparable in this respect with aziminobenzene and benziminazole."

Discussion of the products of interaction of the chlorides (Table I) with ethanol will form part of a further communication. It is known that 1-phenylethyl chloride provides 1-phenylethyl alcohol and styrene on interaction with aqueous formic acid (Hughes, Ingold, and Scott, *loc. cit.*), and that indan-1-ol, indene, and di-1-indanyl ether are the products of hydrolysis of 1-chloroindane (Weisgerber, *Ber.*, 1911, **44**, 1444).

Experimental.

Materials.—Ketones. Acetophenone was carefully fractionated. Its 2-methyl derivative (b.p. 98—99°/25 mm.; semicarbazone, m. p. 205°) was obtained by the addition of *o*-tolunitrile (*Org. Synth.*, Vol. IV, p. 69) to methylmagnesium iodide as described by Baddeley (*J.*, 1944, 235). Addition of aluminium chloride to a solution of mesitylene and acetyl chloride in carbon disulphide (Dittrich and Meyer, *Annalen*, 1891, **264**, 138) provided mesityl methyl ketone (b. p. 120—121°/18 mm.). 1-Tetralone (b. p. 129—130°/12 mm.; semicarbazone, m. p. 217—218°; Kipping and Hunter, *J.*, 1899, 149) was obtained by the oxidation of tetralin with atmospheric oxygen (Brown, Widiger, and Letang, *loc. cit.*) and freed from a little 1-tetralol (phenylurethane, m. p. 120—121°; Brochet and Cornubert, *Compt. rend.*, 1921, **172**, 1499) by oxidation with chromic acid.

Indan-1-one [m. p. 40—41°, from light petroleum; semicarbazone, m. p. 237° (decomp.) from ethanol] was obtained in 83% yield by interaction of β-phenylpropionyl chloride (b. p. 112—115°/15 mm.) and aluminium chloride (Kipping, *J.*, 1894, 480). β-Phenylpropionic acid (m. p. 46—47°, from light petroleum) was obtained by the reduction of ethyl cinnamate in methanolic solution with hydrogen and Raney nickel, and hydrolysis of the product (250 g.) in ethanol (250 c.c.) by addition of a solution of sodium hydroxide (120 g.) in water (150 c.c.). Sodium β-phenylpropionate was filtered off and dissolved in water (1200 c.c.), and the organic acid (190 g.) precipitated by concentrated hydrochloric acid. The recrystallised acid was converted into the acid chloride by interaction with excess of thionyl chloride.

Benzosuberone was prepared from δ-phenyl-*n*-valeryl chloride by a modification of the method described by Kipping and Hunter (*loc. cit.*). Finely powdered aluminium chloride (40 g.) was placed in a three-necked flask fitted with a mercury-sealed stirrer, a reflux condenser closed with a drying tube

($CaCl_2$), and a dropping funnel, and covered with dry ethylene dichloride (150 c.c.). The acid chloride (25 g.) in dry ethylene dichloride (500 c.c.) was added dropwise during 3 hours, with vigorous stirring. When the evolution of hydrogen chloride was complete, the mixture was poured into dilute hydrochloric acid–ice. The organic layer was separated, ethylene dichloride removed on the steam-bath, and the residue distilled with steam. The distillate was extracted with ether, dried (K_2CO_3), and distilled. Benzosuberone (15·5 g.; b. p. 145—146°/12 mm.) was obtained and provided a semicarbazone, m. p. 207—208° (from ethanol), and an oxime, m. p. 107—108° (from light petroleum), as described by Kipping and Hunter (*loc. cit.*). δ-Phenyl-*n*-valeric acid was prepared as follows: cinnamylidenemalonic acid (m. p. 208°) was obtained by condensing cinnamaldehyde with malonic acid (Liebmann, *Ber.*, 1895, **28**, 1439) and converted into its dimethyl ester (m. p. 66—67°; Thiele and Meisenheimer, *Annalen*, 1899, **306**, 253) which was readily hydrogenated over Raney nickel in methanol to dimethyl 3-phenyl-*n*-propylmalonate, b. p. 185—186°/15 mm. [Borsche (*Ber.*, 1912, **45**, 622) employed colloidal palladium.] Sodium hydroxide solution (25%; 625 c.c.) was added to an ice-cold solution of the ester (200 g.) in methanol (2 l.). The sodium salt of the organic acid was collected, washed with methanol, and dissolved in the minimum of water, the solution extracted with ether (2 × 500 c.c.) to remove unchanged ester, and the aqueous layer acidified with sulphuric acid. The mixture was extracted with ether, the extract dried (Na_2SO_4), and the dicarboxylic acid (160 g.; m. p. 96—97°) heated at 120—140° for 6 hours, *i.e.*, until evolution of carbon dioxide was complete. δ-Phenyl-*n*-valeric acid (m. p. 57—58°; Kipping and Hunter, *loc. cit.*, give m. p. 59°) and excess of thionyl chloride provided the acid chloride (b. p. 140—145°/20 mm.).

Secondary alcohols. Mesityl methyl ketone was reduced to the carbinol (m. p. 70—71°; phenylurethane, m. p. 123—124°) by sodium in absolute ethanol as described by Klages and Allendorff (*Ber.*, 1898, **31**, 998). Each of the other ketones was reduced to the corresponding secondary alcohol by aluminium *iso*propoxide in boiling *iso*propyl alcohol in the manner described by Lund (*Ber.*, 1937, **70**, 1520) for the reduction of acetophenone. A rough estimate of the relative rates of reduction under comparable conditions was obtained as follows. Freshly distilled aluminium *iso*propoxide (151 g.; b. p. 140—150°/12 mm.) was dissolved in *iso*propyl alcohol (249 g.); a mixture of this solution (40 g.) and ketone (M/30) was refluxed for 0·5 hour and then distilled at a rate of 1 c.c. of distillate per minute until 20 c.c. had been collected. The acetone in the distillate was converted by excess of the hydrazine in dilute hydrochloric acid into its 2 : 4-dinitrophenylhydrazone which was weighed. The results are assembled in the following table. 1-Phenylethyl alcohol (b. p. 96—97°/12 mm.; phenylurethane m. p. 93—94°) was obtained in 84% yield, 1-tetralol (b. p. 134—136°/15 mm.; phenylurethane m. p. 121—122°) in 76% yield, and *benzosuberol*, m. p. 100—101° (from light petroleum) (Found: C, 81·6; H, 8·6. $C_{11}H_{14}O$ requires C, 81·5; H, 8·6%), in 89% yield. Oxidation by chromic acid in glacial acetic acid provided benzosuberone (semicarbazone, m. p. and mixed m. p. 206—207°).

Ketone.	Wt. of acetone derivative (g.).	Reduction, %.	Relative rate.
Acetophenone	2·33	30	6
Indan-1-one	0·42	5	1
1-Tetralone	0·76	10	2
Benzosuberone	2·36	30	6

Olefins. Reduction of ketones with aluminium *iso*propoxide at higher temperatures is known to provide olefins in some instances (*e.g.*, Bachmann and Struve, *J. Org. Chem.*, 1939, **4**, 461) and we have now observed that the reduction of 1-tetralone in boiling xylene provides 1 : 2-dihydronaphthalene [b. p. 95—97°/15 mm.; dibromide m. p. 69—70° (from light petroleum)] in 72% yield. 1 : 2-Benz*cyclo*hepta-1 : 3-diene was obtained in 25% overall yield as described by Kipping and Hunter (*J.*, 1903, 146): benzosuberone oxime was reduced by sodium amalgam to 3-amino-1 : 2-benz*cyclo*heptene which provided the desired diene (b. p. 120—122°/18 mm.) when the hydrochloride was placed in a bath at 240°.

Chlorides. 1-Phenylethyl chloride and 3-chloro-1 : 2-benz*cyclo*heptene were obtained from the corresponding alcohols by the action of thionyl chloride in the presence of pyridine. In aqueous acetone, 3-chlorobenz*cyclo*heptene provided the corresponding alcohol, m. p. and mixed m. p. 101°. 1-Chloroindane and 1-chlorotetralin were obtained by the addition of dry hydrogen chloride to indene (Haworth, Lindley, and Woodcock, *J.*, 1947, 367) and 1 : 2-dihydronaphthalene respectively at −10°; being sensitive to moisture they were kept in sealed tubes. 1-*o*-Tolylethyl chloride and 1-mesitylethyl chloride were obtained from benzene solutions of the corresponding alcohols by hydrogen chloride. The water formed was removed by calcium chloride. Each chloride was distilled under reduced pressure in an atmosphere of dry nitrogen (cf. appended table).

Compound.	B. p. (0·5 mm.).	Cl, %, found.	Cl, %, calc.	Compound.	B. p. (0·5 mm.).	Cl, %, found.	Cl, %, calc.
1-Phenylethyl chloride	39—40°	25·2	25·3	1-Chloroindane	68—69°	23·0	23·3
1-*o*-Tolylethyl chloride	96—97 (15 mm.)	22·8	23·0	1-Chlorotetralin	76—77	21·2	21·3
1-Mesitylethyl chloride	83—84	19·2	19·45	3-Chlorobenz*cyclo*heptene	95—96	19·6	19·65

Physical Data.—The ultra-violet absorption spectra of most of the ketones and olefins employed in this work were measured with a Hilger E3 quartz spectrograph fitted with a Spekker photometer. A tungsten-steel high-tension spark was employed as the source of light. Immediately before use, each substance was either recrystallised or redistilled under reduced pressure. Relevant data from other sources are also assembled; our own are given in parentheses.

Compound.	$\lambda_{max.}$, A.	$\varepsilon_{max.}$	Ref.	Raman frequency for the carbonyl group (cm.$^{-1}$).	Ref.
1-Indanone	2350 (2400)	12,000 (11,000)	(*a*)	1714 *	(*c*)
1-Tetralone	2400 (2450)	10,000 (11,000)	(*a*)	1682	(*c*)
Benzosuberone	2350 (2400)	9,000 (9,000)	(*a*)	1676	(*c*)
Acetophenone	2400 (2350)	12,000 (10,000)	(*b*)	1684	(*c*)
2 : 4 : 6-Trimethylacetophenone	2400 †	4,000	(*b*)	1700	(*d*)

* This frequency is as high as that for a carbonyl group which is not conjugated with a benzene ring (cf. benzyl methyl ketone, 1714 cm.$^{-1}$), but is not evidence of lack of conjugation as the frequency for indan-2-one is also abnormally high (1739 cm.$^{-1}$; cf 2-tetralone, 1717 cm.$^{-1}$).

† Maximum absorption occurs at a shorter wave-length.

	Semicarbazones.		Oximes [Ref. (*e*)].	
	$\lambda_{max.}$, A.	$\varepsilon_{max.}$	$\lambda_{max.}$, A.	$\varepsilon_{max.}$
I-Indanone	(2705)	(18,000)	2500	10,000
1-Tetralone	(2800)	(18,000)	2500	10,000
Benzosuberone	(2650)	(17,000)	2450	10,000
Acetophenone	(2750)	(18,000)	2500	10,000

	$\lambda_{max.}$, A.	$\varepsilon_{max.}$	Ref.
Indene	2500	10,000	(*f*)
1 : 2-Dihydronaphthalene	2500	10,000	(*f*)
1 : 2-Benz*cyclo*hepta-1 : 3-diene	(2550)	(10,000)	
Styrene	2460	10,000	(*f*)

(*a*) Ramart-Lucas and Hoch, *Bull. Soc. chim.*, 1935, [v], **2**, 327; 1938, [v], **5**, 848. (*b*) O'Shaughnessy and Rodebush, *J. Amer. Chem. Soc.*, 1940, **62**, 2906. (*c*) Bicquard, *Bull. Soc. chim.*, 1941, [v], **8**, 55. (*d*) Saunders, Murray, and Cleveland, *J. Amer. Chem. Soc.*, 1941, **63**, 3121. (*e*) Ramart-Lucas and Hoch, *Bull. Soc. chim.*, 1938, [v], **5**, 987. (*f*) Morton and de Gouveia, *J.*, 1934, 911, 916.

Rates of Semicarbazone Formation.—The method was based on that described by Conant and Bartlett (*J. Amer. Chem. Soc.*, 1932, **54**, 2881). A solution (0·200M.; 60 c.c.) of the ketone in ethanol and a mixture of an aqueous solution (0·200M.; 30 c.c.) of semicarbazide hydrochloride and an aqueous solution (0·400M.; 30 c.c.) of potassium acetate were placed in a thermostat at 25·0° or 41·0° and subsequently mixed together. Samples (10 c.c.) were removed after selected intervals of time and unchanged semicarbazide determined by titration with iodine solution. The reaction is reversible and the bimolecular velocity constants (k_2) were obtained by substitution in the equation:

$$k_2 = [138/(t - t_1)Z] \log_{10}(2S + A)(2S_1 + B)/(2S + B)(2S_1 + A).$$

S, the concentration of semicarbazide at time t, is given by $0{\cdot}025T$ where T is the titre, expressed in c.c. N/10-iodine solution, of 10 c.c. of reaction mixture. $A = (0{\cdot}05 + RS_\infty + Z)$, $B = (0{\cdot}05 + RS_\infty - Z)$, $Z = [(0{\cdot}05 + RS_\infty)^2 + 0{\cdot}2RS_\infty]^{1/2}$, $R = (0{\cdot}05 + S_\infty)/(0{\cdot}05 - S_\infty)$, and the subscripts have their usual significance. This equation assumes pseudo-unimolecular hydrolysis of the semicarbazone (velocity constant k_1) and gives values of k_1 which are somewhat lower than those obtained by applying Conant and Bartlett's equation. Details of a typical experiment are given in Table II, and the velocity constants are assembled in Table III.

TABLE II.

Interaction of acetophenone and semicarbazide at 25·0°.

Directly measured end-point, $T_\infty = 0{\cdot}82$; $T_0 = 20{\cdot}00$ c.c.

$(t - t_1)$, min.	0	21	40	60	80	103	127
T, c.c.	17·82	15·02	13·00	11·34	9·88	8·48	7·36
k_2	—	5·40	5·40	5·33	5·39	5·45	5·43

Mean value of $k_2 = 5{\cdot}41$ hr.$^{-1}$ g.-mol.$^{-1}$ l. at 25·0°.
$k_1 = k_2RS_\infty = 0{\cdot}0123$ hr.$^{-1}$ at 25·0°.

TABLE III.

Velocity constants.

Compound.	Temp.	k_2, hr.$^{-1}$ g.-mol.$^{-1}$ l.	k_1, hr.$^{-1}$.	Compound.	Temp.	k_2, hr.$^{-1}$ g.-mol.$^{-1}$ l.	k_1, hr.$^{-1}$.
Acetophenone	25·0°	5·41	0·0123	1-Tetralone	25·0°	1·03	0·0169
	41·0	7·9	0·0223		41·0	2·00	0·0337
1-Indanone	25·0	1·40	0·0167	Benzosuberone	25·0	0·59	0·0164
	41·0	3·29	0·0391		41·0	1·03	0·0253

Ethanolysis of the Chlorides.—One batch of absolute alcohol, obtained by the method of Lund and Bjerrum (*Ber.*, 1931, **64**, 210), was used for the entire investigation and was redistilled from magnesium ethoxide before each experiment. The chlorides provided hydrogen chloride which was determined conductometrically or by titration with a solution of sodium ethoxide in absolute ethanol (lacmoid indicator). These two methods gave comparable results but the former was the more accurate and the

more convenient. Although the conductivities of solutions of hydrogen chloride in absolute ethanol have been determined by a number of workers (*e.g.*, Lapworth and Partington, *J.*, 1911, 1426; Partington, *J.*, 1911, 1939; Goldschmidt, *Z. physikal. Chem.*, 1914, **89**, 129), we calibrated our conductivity cell by introducing ethanolic solutions of hydrogen chloride of known concentration and measuring the conductivities at 0·0° and again at 25·0° (cf. Norris *et al.*, *J. Amer. Chem. Soc.*, 1928, **50**, 1795; 1935, **57**, 1415). Resistances were measured on a Universal Impedance Bridge of the Dawe Instrument Co. Ltd., kindly provided by Imperial Chemical Industries Ltd. It was energised by a 1000-cycle audio-oscillator, and the system was sensitised by a variable condenser in parallel with the conductivity tube. The same tube subsequently constituted reaction vessel and conductivity cell. It had lightly platinised electrodes which did not need to be re-platinised during the course of the work. The electrode unit was attached to the tube by a ground-in joint. Measurements made under nitrogen did not differ by more than the experimental error from those obtained in air (cf. Norris *et al.*, *loc. cit.*). Solutions of hydrogen chloride in ethanol, and solutions in which ethanolysis of a chloride was complete, showed no variation in conductivity when kept under air at 0·0° or 25·0° for several days. Hughes, Ingold, and Scott (*loc. cit.*) observed a ready reaction between ethanol and hydrogen chloride at 70°.

General Experimental Procedure.—The conductivity cell, charged with absolute ethanol (10 c.c.), was placed in the thermostat and after *ca.* 20 minutes a volume, selected to provide an approx. 0·05M-solution, of the chloride was added and the mixture vigorously agitated. A stop watch was started as the first conductivity measurement was made and further measurements were made at selected intervals of time. When the reaction was complete, or when a sufficient range of readings had been obtained (usually after 24 hours), a sample (5 c.c.) was pipetted into 50% aqueous acetone (20 c.c.), refluxed gently for 30 minutes, and titrated with standard alkali. The molarity of the ethanolic solution was calculated from the titre and agreed with that obtained conductometrically in those instances where the reaction went to completion in the conductivity cell. A detailed example is shown in Table IV.

Actually, owing to the presence of the aromatic material, the concentrations of hydrogen chloride as determined by the conductivity method were about 3% low. This discrepancy was also observed by Norris.

Ethanolysis in the Presence of Sodium Ethoxide.—If the ethanolysis is bimolecular, the rate of reaction should be greatly increased by the presence of ethoxide ions: no such effect has been found. The conductivity cell was charged with absolute ethanol (10 c.c.) and 0·100N-sodium ethoxide (0·500 c.c.) and placed in a thermostat at 25·0°. After 20 minutes, the chloride (*ca.* 0·0010 mole) was added and the resistance measured at frequent intervals. As previously described, change in resistance indicated when the reaction mixture was neutral and the time was then recorded. Further additions of 0·100N-sodium ethoxide solution were made from a micro-burette, precautions being taken to prevent access to atmospheric moisture, and the intervals of time to reach neutrality were recorded. The final titration was obtained by washing the reaction mixture into a flask with 50% aqueous acetone (20 c.c.) and titration with sodium ethoxide solution. A detailed example is shown in Table V.

TABLE IV.

Ethanolysis of 1-*chlorindan at* 25·0°.

The chloride (0·16 c.c.) was added to ethanol (10 c.c.).

Time (mins.).	Conductance (mhos × 10^4).	Molarity of HCl.	$10^4 k$ (mins.$^{-1}$).	Time (mins.).	Conductance (mhos × 10^4).	Molarity of HCl.	$10^4 k$ (mins.$^{-1}$).
0	2·47	0·0032	—	87	26·60	0·0612	89
12	8·00	0·0142	90	103	28·17	0·0663	86
21	11·24	0·0211	87	120	30·30	0·0727	87
37	15·87	0·0325	86	139	32·15	0·0765	83
57	20·62	0·0446	85	153	33·33	0·0832	89
				After 24 hours	39·50	0·1105	—
73	24·15	0·0541	88	Final molarity by titration		0·115	—

Mean value of k = 0·0087 mins.$^{-1}$ at 25·0°.

TABLE V.

Ethanolysis of 1-*chlorindan at* 25·0° *in the presence of small concentrations of sodium ethoxide.*

0·1N-NaOEt, c.c.	0·50	1·50	3·00	4·00	5·00	6·00	7·00	8·00	11·00
Time (mins.)	5·5	17	38	53	70	92	118	152	∞
$10^4 k$	84	87	84	85	86	86	86	85	—

Mean value of k = 0·0085 mins.$^{-1}$ at 25·0°.

The Chlorides and Potassium Iodide in Acetone.—Potassium iodide (AnalaR) was recrystallised twice from distilled water, thoroughly dried in an oven at 120°, and stored in the dark in air-tight containers. Acetone (2 l.) was refluxed for 6 hours over potassium permanganate (20 g.) and sodium hydroxide (20 g.) and fractionally distilled. The fraction of b. p. 56·5—57·0° was collected separately and access to moisture was prevented. Each chloride (0·01 mole) in turn was added to a 0·04M-solution (50 c.c.) of potassium iodide in acetone; samples (5 c.c.), in sealed tubes, were placed in a thermostat at 100·0°. In each instance there was no precipitate of potassium chloride after several hours. Precipitation was apparently complete after 30 minutes when benzyl chloride was employed.

FACULTY OF TECHNOLOGY, UNIVERSITY OF MANCHESTER. [*Received, August 16th*, 1950.]

81. *The (+)- and (−)-o-Tolyl-p-tolylcarbinols.*

By M. P. Balfe, M. K. Hargreaves, and J. Kenyon.

Resolution of *o*-tolyl-*p*-tolylcarbinol into its optical antipodes has been achieved by fractional crystallisation of the quinine and the strychnine salts of its hydrogen phthalate. Some reactions of the acid ester are described.

Recrystallisation of the quinine salts of (±)-*o*-tolyl-*p*-tolylcarbinyl hydrogen phthalate yields the optically pure (−)-hydrogen phthalate. The pure (+)-hydrogen phthalate is obtained by converting the more soluble quinine salt into the corresponding strychnine salt which is, in turn, recrystallised. Decomposition of the (+)- and the (−)-hydrogen phthalate yields respectively the (+)- and the (−)-carbinol.

o-Tolyl-*p*-tolylcarbinyl hydrogen phthalate reacts with dilute sodium hydroxide solution and with sodium toluene-*p*-sulphinate in a manner similar to, but considerably slower than, that of *p*-methoxydiphenylcarbinyl hydrogen phthalate (Part II, *J.*, 1942, 605). The reaction between the hydrogen phthalate and anhydrous formic acid affords the di-(*o*-tolyl-*p*-tolylcarbinyl) ether.

Experimental.

o-*Tolyl* p-*Tolyl Ketone.*—A mixture of *o*-toluoyl chloride (80 g.), anhydrous aluminium chloride (80 g.), and dry toluene (320 g.) was warmed for 2 days on the water-bath and then set aside for a week, and the complex decomposed with ice and hydrochloric acid. The dried toluene layer was distilled, and the fraction, b. p. 181—182°/18 mm., collected. With care the material so prepared is obtained colourless, and has $n_D^{20\cdot9}$ 1·5908 (cf. Scharwin and Schorygin, *Ber.*, 1903, **36**, 2025); the yield is up to 105 g. (67—96%).

o-*Tolyl*-p-*tolylcarbinol.*—(a) *From o-tolyl p-tolyl ketone by Pondorff's method.* Cleaned aluminium (11 g.) and mercuric chloride (0·5 g.) were added to dry *iso*propyl alcohol (120 c.c.). After 2·5 hours *iso*propyl alcohol (120 c.c.) was added and, when all the aluminium had dissolved, *o*-tolyl *p*-tolyl ketone (41·3 g.) dissolved in *iso*propyl alcohol (200 c.c.) was added. After separation of acetone in the usual manner the carbinol (18 g., 43%) was isolated by extraction with ether.

(b) *By Grignard's method.* *o*-Tolyl bromide (20 g.), dissolved in an equal volume of dry ether, was slowly run on to magnesium (3 g.) covered with dry ether. When reaction had ceased, an ethereal solution of *p*-tolualdehyde (14 g.) was run in slowly with vigorous stirring. On completion of the reaction, the mixture was poured on ice and ammonium chloride; the yield was 5 g. (20%). The (±)-o-*tolyl*-p-*tolylcarbinol* separated from light petroleum in rhombs, m. p. 59—60° (Found: C, 84·6; H, 7·5. $C_{15}H_{16}O$ requires C, 84·9; H, 7·6%).

(±)-o-*Tolyl*-p-*tolylcarbinyl α-naphthylurethane.* A mixture of the carbinol (5·25 g.) and α-naphthyl *iso*cyanate (4 g.) was warmed for a few minutes and set aside. The resulting *urethane*, after recrystallisation from light petroleum and then from ethanol, formed needles, m. p. 124° (Found: N, 3·4. $C_{26}H_{23}O_2N$ requires N, 3·7%).

(±)-o-*Tolyl*-p-*tolylcarbinyl* p-*nitrobenzoate.* A solution of the carbinol (9·3 g.) and *p*-nitrobenzoyl chloride (9·5 g.) in dry pyridine (10 c.c.) and carbon tetrachloride (20 c.c.) slowly deposited the *ester*, which separated from alcohol in fine needles (10·2 g.), m. p. 117—118° (Found: N, 3·4. $C_{22}H_{19}O_4N$ requires N, 3·8%).

(±)-o-*Tolyl*-p-*tolylcarbinyl Hydrogen Phthalate.*—A solution of *o*-tolyl-*p*-tolylcarbinol (106 g.) and phthalic anhydride (74 g.) in pyridine (40 g.) and toluene (40 g.) was warmed, set aside for 14 days, and then extracted with ice-cold hydrochloric acid; (±)-*o*-tolyl-*p*-tolylcarbinyl hydrogen phthalate (180 g.) crystallised from the toluene solution. The crude hydrogen phthalate (132 g., 72%) was freed from phthalic acid by extraction with chloroform. The *ester* after three crystallisations from ether–light petroleum formed prisms, m. p. 129° (Found, by rapid titration with dilute NaOH: *M*, 362. $C_{23}H_{20}O_4$ requires *M*, 360).

(−)-o-*Tolyl*-p-*tolylcarbinyl Hydrogen Phthalate.*—A solution of the (±)-hydrogen phthalate (124 g.) and quinine (111·6 g.) in hot ethanol was allowed to cool and diluted with water to incipient crystallisation. The quinine salt (94 g.) of (−)-*o*-tolyl-*p*-tolylcarbinyl hydrogen phthalate slowly crystallised. After four recrystallisations from ethanol (96%) it was decomposed by addition of ice-cold 5*N*-hydrochloric acid to a suspension of the salt in acetone, the mixture was then extracted with ether, and the ethereal extract washed with dilute hydrochloric acid and then with water and dried. The hydrogen phthalate separated from ether–light petroleum in small rhombs, m. p. 126°, $[\alpha]_D^{17}$ −49·7° (*l*, 2; *c*, 2·000 in chloroform). Further recrystallisation from carbon disulphide produced no significant change in the rotatory power.

(+)-o-*Tolyl*-p-*tolylcarbinyl Hydrogen Phthalate.*—The mother-liquor from the first crop of quinine salt was decomposed, yielding (+)-*o*-tolyl-*p*-tolylcarbinyl hydrogen phthalate (48 g.) having $[\alpha]_D^{17}$ +20° in chloroform. This acid ester (48 g.) and strychnine (42 g.) were dissolved in boiling 96% ethyl alcohol, and the solution was cooled and diluted with water. After ½ hour, crystals (m. p. 120—122°; 44 g.) of the strychnine salt of (+)-*o*-tolyl-*p*-tolylcarbinyl hydrogen phthalate were deposited. This salt was recrystallised twice from 96% alcohol, then decomposed as described above. The resulting (+)-*o*-tolyl-

p-tolylcarbinyl hydrogen phthalate separated from carbon disulphide in needles, $[\alpha]_D^{18\cdot6}$ +49·4° (*l*, 2; *c*, 2·000 in chloroform). Its specific rotatory powers in various solvents were as follows:

Solvent.	*l.*	*c.*	$[\alpha]_D^{20}$.	Solvent.	*l.*	*c.*	$[\alpha]_D^{20}$.
Acetic acid	1	3·40	+27·1°	Chloroform	2	2·00	49·7°
Acetone	2	1·50	29·7	Benzene	2	1·80	61·0
Ethyl alcohol	2	1·80	30·9				

(+)- *and* (−)-o-*Tolyl*-p-*tolylcarbinols.*—(−)-*o*-Tolyl-*p*-tolylcarbinyl hydrogen phthalate, $[\alpha]_D^{17}$ −49·7° (2 g.), was added to a solution of sodium ethoxide [from sodium (0·6 g.) in warm 96% alcohol (15 g.)]. The mixture was heated on a steam-bath for some minutes, until a thick white precipitate was produced. After being cooled in ice the product was diluted with water, and the carbinol (0·6 g.) filtered off and recrystallised from ether–light petroleum; it formed needles, m. p. 47—48°, $[\alpha]_D^{21}$ −25·2° (*l*, 2; *c*, 0·600 in carbon disulphide). The (+)-carbinol (0·6 g.), similarly obtained from the (+)-hydrogen phthalate (2 g.) of $[\alpha]_D^{18\cdot6}$ +49·4°, formed prisms, m. p. 48—49°, $[\alpha]_D^{20}$ +24·1° (*l*, 2; *c*, 1·100 in carbon disulphide).

Some Reactions of o-*Tolyl*-p-*tolylcarbinyl Hydrogen Phthalate.*—(1) *With sodium toluene*-p-*sulphinate.* Sodium toluene-*p*-sulphinate (0·75 g.), dissolved in 20 c.c. of water, was added to the hydrogen phthalate (1·5 g.) in 8 c.c. of a saturated solution of sodium hydrogen carbonate, and the mixture warmed on the steam-bath. After ½ hour, needles (0·8 g.) of p-*tolyl* o-*tolyl*-p-*tolylcarbinyl sulphone* were deposited which, after recrystallisation from alcohol and then twice from acetic acid, had m. p. 152—152·5° (Found: C, 75·15; H, 6·5; S, 8·7. $C_{28}H_{24}O_2S$ requires C, 75·4; H, 6·3; S, 9·1%). At room temperature a similar reaction takes some 16 weeks for completion.

Sodium toluene-*p*-sulphinate (0·09 g.) in N-sodium hydroxide (0·5 c.c.) was added to (+)-*o*-tolyl-*p*-tolylcarbinyl hydrogen phthalate ($[\alpha]_D^{19}$ +20°; 0·18 g.) dissolved in 96% ethyl alcohol (10 c.c.). The rotatory power of the solution changed as follows (*l*, 2; *t*, 20°):

Time, days	0	0·25	1	2	3	4	11	22	34
α	0·54°	0·51°	0·46°	0·45°	0·44°	0·43°	0·41°	0·37°	0·31°

After 34 days the mixture was warmed on the steam-bath, it racemised within 2 hours.

(2) *With anhydrous formic acid.* A solution of (±)-*o*-tolyl-*p*-tolylcarbinyl hydrogen phthalate (2 g.) in anhydrous formic acid (30 g.), after being kept for several hours, was poured into ice-water and extracted with ether. The ethereal extract was washed several times with aqueous sodium hydroxide, then dried, and the ether removed until crystals of *di*-(o-*tolyl*-p-*tolylcarbinyl*) *ether* separated (0·11 g.) as needles, m. p. 138—139° (Found: C, 88·4; H, 7·5. $C_{30}H_{30}O$ requires C, 88·7; H, 7·35%). When (+)-*o*-tolyl-*p*-tolylcarbinyl hydrogen phthalate ($[\alpha]_D^{19}$ +20° in chloroform; 0·23 g.) was dissolved in anhydrous formic acid (10 c.c.), racemisation was complete in 20 minutes.

(3) *With dilute sodium hydroxide solution.* A solution of (±)-*o*-tolyl-*p*-tolylcarbinyl hydrogen phthalate (1·6 g.) in 0·3N-sodium hydroxide solution (10 c.c.) on storage deposited *di*-(*o-tolyl*-p-*tolylcarbinyl*) *phthalate* (1·0 g.) as needles, m. p. 117·5° (Found: C, 82·2; H, 6·0. $C_{38}H_{34}O_4$ requires C, 82·3; H, 6·1%).

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82. *Alkyl–Oxygen Fission in Carboxylic Esters. Part VI. Solvolytic Reactions of Esters of Optically Active* cyclo*Hexylphenyl-, Methylphenyl-, and Methyl-α-naphthyl-carbinols.*

By M. P. BALFE, G. H. BEAVEN, and J. KENYON.

First-order rate constants for reactions of the hydrogen phthalate, acetate, and formate of optically active *cyclo*hexylphenylcarbinol (I) with carboxylic acids are compared with constants for similar reactions of esters of methylphenyl- (II) and methyl-α-naphthylcarbinols (III). All these reactions are accompanied by racemisation. The tendency to undergo this kind of reaction (alkyl–oxygen fission) is a little less in (I) than in (II), and greatest in (III).

(+)-*cyclo*HEXYLPHENYLCARBINYL HYDROGEN PHTHALATE was prepared as described by Levene and Mikeska (*J. Biol. Chem.*, 1927, **75**, 587), and the corresponding (−)-ester by crystallisation of the strychnine salt of the residual lævorotatory ester. The (+)-phthalate gives the (+)-carbinol on hydrolysis with alkali: from the (+)-carbinol, the (+)-acetate (pyridine–acetic

anhydride), (−)-benzoate (pyridine–benzoyl chloride), and (+)-formate (formic–acetic anhydride) are obtained. The rotatory powers and other characteristics of these compounds are recorded in Table I.

Rate constants for esterifications of the carbinol (Table IV) are derived from changes in rotatory power during the reaction. They are all first-order as the reagent was in excess. The presence of pyridine increases the rate constant of the reaction with acetic anhydride by

TABLE I.

(+)-cyclo*Hexylphenylcarbinol and its esters.*

	M. p.	B. p.	n_D^t.	$[\alpha]_D^{20}$.	Solvent.	*c.*
Carbinol	72°	—	—	+22·5°	EtOH	5·13
				38·8	Et_2O	4·03
Hydrogen phthalate	127	—	—	22·0	EtOH	5·00
				51·8	$CHCl_3$	2·22
Acetate	—	170°/20 mm.	1·5125/20°	71·0	EtOH	3·98
Formate	—	180/15 mm.	1·5240/17	75·4	EtOH	2·31
Benzoate	82	—	—	−32·2	EtOH	2·10

TABLE II.

Solvolytic reactions of esters of cyclo*hexylphenyl-, methylphenyl-,* and *methyl-α-naphthylcarbinols.*

(For concentrations and solvent proportions see Experimental section.)

			First-order k * × 10^5 (in min.$^{-1}$) in reaction of ester of:		
Ester.	Solvent.	Temp.	*cyclo*Hexylphenylcarbinol.	Methylphenylcarbinol.	Methyl-α-naphthylcarbinol.
Acetate	AcOH	18°	0	—	—
		100	5	—	—
	AcOH–H_2O	18	0	—	—
		100	70	—	—
	AcOH–*p*-$C_6H_4Me{\cdot}SO_3Na$	100	35	—	—
	$H{\cdot}CO_2H$	—	940 at 17°	740 at 19° 2900 at 27°	11,000 at 15° 63,000 at 21°
Formate	AcOH	100	0	—	—
	AcOH–H_2O	20	0	1·0	—
	$H{\cdot}CO_2H$	21	1200 †	2500	—
		26	1700 ‡		
Benzoate	AcOH	20°	—	0	0
		hot	—	0 at 100°	70 at 80°
	AcOH–H_2O	100	—	250	—
Hydrogen phthalate	AcOH–H_2O	100	0	0	100
		23	0	—	—
		100	250	1200	1250
	AcOH–NO_2Me	100	4	—	—
	$H{\cdot}CO_2H$	20—45	i	i	i
	MeOH or EtOH	reflux	0	0	0
	MeOH–H_2O	reflux	0	0	60
	EtOH–H_2O	reflux	0	0	50

* 0 = No change in rotatory power during long period; i = too rapid for measurement.
† Table V. ‡ From second branch of mutarotation curve, Table IV.

a factor of 10^3; the reaction with formic acid is some 100-fold as fast as the reaction with formic–acetic anhydride.

With thionyl chloride and phosphorus pentachloride (in the absence and in the presence of pyridine) and with aqueous hydrochloric acid, the (+)-carbinol gives partly racemised (+)-chlorides.

First-order rate constants for solvolytic reactions of some of the esters are given in Table II, together with first-order constants for similar reactions of methylphenylcarbinol and methyl-α-naphthylcarbinol, calculated from the data recorded by Balfe *et al.* (*J.*, 1946, 797). It is evident that in the sequence of alcohols arranged in order of diminishing tendency of their esters to react by alkyl–oxygen fission (Balfe *et al.*, *J.*, 1946, 803), *cyclo*hexylphenylcarbinol falls just below methylphenylcarbinol. The present results agree with those previously

reported (*J.*, 1946, 803) in showing that the solvolytic reaction occurs much more readily in acid solvents (particularly formic acid) than in alcohols, and is promoted by addition of water to the medium. Solvolysis of *cyclo*hexylphenylcarbinyl acetate is accelerated by addition of a salt (sodium toluene-*p*-sulphonate) to the medium, and solvolysis of the hydrogen phthalate by addition of nitromethane: presumably, these effects are related to increases in the dielectric constants of the media.

In agreement with the comparatively small tendency to reaction by the alkyl–oxygen fission mechanism in esters of *cyclo*hexylphenylcarbinol, it is found that the carbinol is obtained optically pure on hydrolysis of its hydrogen phthalate by weak alkali (*e.g.*, sodium carbonate solution), a reagent which gives rise to a partly racemised product in the hydrolysis of the hydrogen phthalate of carbinols which have a strong tendency to react by this mechanism (*J.*, 1946, 807).

The hydrogen phthalates of the carbinols described above, when dissolved in an equimolecular proportion of aqueous sodium hydroxide, do not yield the neutral ester and do not react with sodium toluene-*p*-sulphinate, as is to be expected in view of their comparatively small tendency to react by the mechanism which involves alkyl–oxygen fission. α-Naphthylphenylcarbinyl hydrogen phthalate also does not undergo these reactions: it has not been possible to obtain it in optically active forms for study of its solvolytic reactions by the methods described above.

Experimental.

*cyclo*Hexylphenylcarbinol (prepared by Grignard reaction from *cyclo*hexyl bromide; 25% yield) had m. p. 50°; von Auwers and Treppmann (*Ber.*, 1915, **48**, 1220) record m. p. 50—50·5°. Its (±)-hydrogen phthalate, recrystallised from ethyl alcohol, had m. p. 163—164° (Levene and Mikeska, *loc. cit.*, record m. p. 163°) (Found: equiv. by titration with 0·1N-NaOH, 339. Calc. for $C_{21}H_{22}O_4$: equiv., 338). The cinchonidine salt was recrystallised four times from chloroform–acetone (3 : 1), which raised the rotatory power of the hydrogen phthalate to the maximum value. Levene and Mikeska extracted the solid salt twice with hot acetone and recrystallised the hydrogen phthalate, obtained from the residual salt, from ether. The present procedure gives a product of slightly higher rotatory power. The (−)-hydrogen phthalate, recovered from the mother-liquors, was converted into the strychnine salt, from which, after one recrystallisation from methyl alcohol–acetone (4 : 1), the strychnine salt of the optically pure (−)-hydrogen phthalate was obtained. Cinchonidine was removed by treating its salt, suspended in acetone, with dilute hydrochloric acid and dilution with cold water: the (+)-hydrogen phthalate separated and solidified. Strychnine was precipitated from its salt, in hot ethyl-alcoholic solution, by addition of dilute aqueous ammonia; the filtrate was acidified with dilute hydrochloric acid, and the (−)-hydrogen phthalate separated and solidified. Both the (+)- and the (−)-hydrogen phthalate were obtained in about 35% yield on the (±)-phthalate used. The (+)- and the (−)-carbinol were obtained from the hydrogen phthalates by steam-distillation from 5N-aqueous sodium hydroxide. Steam-distillation from 1N-sodium carbonate, sodium hydroxide, or sodium ethoxide (in ethyl alcohol) yielded carbinols of the same rotatory power as that from 5N-sodium hydroxide.

Esters were prepared by usual methods (see also p. 376). The (+)-*acetate* had b. p. 162—166°/20 mm., n_D^{25} 1·5106, n_D^{20} 1·5131 (Found: 1·000 g. required 242 mg. of KOH for hydrolysis. $C_{15}H_{20}O_2$ requires 242 mg.). The (±)-*formate* was obtained from a solution of (+)-carbinol in anhydrous formic acid after 27 days (the solution then being optically inactive); b. p. 169—172°/22 mm., n_D^{25} 1·5250 (Found: 1·000 g. required 219 mg. of KOH for hydrolysis. $C_{14}H_{18}O_2$ requires 218 mg.). The (±)-*benzoate*, recrystallised from ether–light petroleum, had m. p. 99° (Found: 1·000 g. required 297 mg. of KOH for hydrolysis. $C_{20}H_{22}O_2$ requires 294 mg.). The carbinol did not react with toluene-*p*-sulphonyl chloride. The (±)-*chloride* [prepared by slow addition of thionyl chloride (5 mols.) to the (±)-carbinol; solution heated for 1 hour, then treated in usual way] had m. p. 27—29°, b. p. 146—148°/15 mm., n_D^{17} 1·5425 (Found: Cl, 16·9. $C_{13}H_{17}Cl$ requires Cl, 17·0%). Constants of the optically active esters are in Table I. Steam-distillation of a solution of the (−)-benzoate in 5N-sodium hydroxide gave the carbinol with $[\alpha]_D^{20}$ +22·0° in ethyl alcohol, *i.e.*, substantially the same as that from which the benzoate was prepared.

Optically active chlorides (*cyclo*hexylphenylchloromethanes) were prepared from (+)- or (−)-carbinols (Table I) unless otherwise stated. During distillation, the chlorides suffered some racemisation, apparently not caused by decomposition since chlorine contents were satisfactory. Levene and Mikeska (*loc. cit.*), from carbinols of lower optical purity, obtained chlorides with proportionally higher rotatory powers, probably on account of lower distillation temperatures (b. p. *ca.* 110°/1 mm.).

Optically active chlorides were prepared as follows (see Table III for physical constants). (*a*) 1·4 G. of (+)-carbinol, 1 c.c. of thionyl chloride, procedure as above. (*b*) 2·5 G. of (−)-carbinol and 2·4 g. of pyridine (2 mols.), 1·3 c.c. of thionyl chloride added, procedure as above. (*c*) 2·5 G. of (−)-carbinol were added gradually to a suspension of phosphorus pentachloride (4·2 g., 1 mol.) in ether (50 c.c.) at 0°; after 3 hours at room temperature, the product was isolated in the usual way. (*d*) 2·5 G. of (−)-carbinol with 2·4 g. pyridine (2 mols.) were added to 4·2 g. of phosphorus pentachloride (2 mols.), and then treated as in (*c*). (*e*) 2·0 G. of carbinol, $[\alpha]_D^{20}$ −20·6° (in EtOH), were triturated with 10 c.c. of 10N-hydrochloric (10 mols.): the oil solidified, 1·7 g. of recrystallised chloride being obtained.

Rate Constants.—Individual values of k were calculated from the rotation changes for each time interval. They fall in a satisfactory distribution about the mean, which was also confirmed by calculation

of k from the time of half-reaction, read from a straight line drawn through log α–time plots. Rate constants for the reactions of the acetates of methylphenyl- and methyl-α-naphthyl-carbinols are taken from Downer (Thesis, London, 1942): they are supported by calculation from half-reaction time. For other reactions of these two carbinols the constants are calculated only from half-reaction times interpolated in the data of Balfe *et al.* (*J.*, 1946, 797), the observations being inadequate for calculation of individual constants: they cannot be of a high order of accuracy, but are probably adequate for the present comparative use. [The data given by Balfe *et al.* (*J.*, 1946, 797) for the reaction of (+)-methylphenylcarbinyl acetate with formic acid were erroneously transcribed: to all the observations at 19°, except the first, add 2·0° to each α; to all the observations at 27°, except the first, add 0·5° to each α.]

Table IV summarises the data for the formation of esters, and Table V the data for solvolytic reactions. In the reaction of (+)-carbinol with formic acid, the rotatory power first rises (formation

TABLE III.

(±)- *and* (−)-cyclo*Hexylphenylchloromethane.*

	Crude chloride.			Redistilled chloride.				
	Yield, %	$[\alpha]_D^t$ in Et_2O.	n_D^t.	B. p.	$[\alpha]_D^t$ in Et_2O:	c.	n_D^t.	M. p.
(*a*)	98	+44·8°/15°	1·544/15°	144°/14 mm.	+39·1°/15°	1·4	—	30°
(*b*)	87	−62·0°/18°	1·546/18°	145°/15 mm.	−30·8°/19°	1·4	1·544/19°	30
(*c*)	96	−2·9°/19°	1·541/19°	—	−0·76°/19°	1·4	1·543/19°	27—30
(*d*)	93	−4·5°/18°	1·541/18°	138°/20 mm.	−1·7°/18°	1·5	1·544/18°	29—30
(*e*)	84	—	—	—	−15·7°/20°	7·0	—	28

TABLE IV.

Formation of esters of cyclo*hexylphenylcarbinol.*

Carbinol, g.	Reactants.	Temp.	Initial α (l, 2 dm.).	1st-Order k: Mean.	From $t_{\frac{1}{2}}$.	$t_{\frac{1}{2}}$, mins.
1·55	Ac_2O (10 c.c.); pyridine (15 c.c.)	23°	+5·28°	$2·3 \times 10^{-4}$	$2·2 \times 10^{-4}$	31
1·195	Ac_2O (25 c.c.)	21	+2·53	$7·6 \times 10^{-5}$	$7·4 \times 10^{-5}$	9300
1·07	HCO·OAc (15 c.c.)	23	+4·47	$1·1 \times 10^{-4}$	$1·2 \times 10^{-4}$	6000
1·00	$H·CO_2H$ (25 c.c.)	26	+1·88	$5·5 \times 10^{-4}$ *	—	13

* Corrected for racemisation of formate.

TABLE V.

Solvolytic reactions of esters of cyclo*hexylphenylcarbinol.*

Ester.	Reactant.	Temp.	Initial α_D^{20} (2 dm.).	1st-Order k, in min.$^{-1}$. Mean.	From $t_{\frac{1}{2}}$.	$t_{\frac{1}{2}}$
Acetate ($[\alpha]^{18}$ +66° in EtOH), 3·01 g.	AcOH (100 c.c.)	100°	+2·78°	$5·0 \times 10^{-5}$	$4·8 \times 10^{-5}$	242 hrs.
Acetate, as above, 2·30 g.	AcOH (90 c.c.) + H_2O (10 c.c.)	100	+3·88	$7·2 \times 10^{-4}$	$7·0 \times 10^{-4}$	16·5 ,,
Acetate, as above, 1·72 g.	AcOH (100 c.c.) + *p*-$C_6H_4Me·SO_3Na$ (14·4 g.)	100	+2·73	$3·5 \times 10^{-4}$	$3·5 \times 10^{-4}$	33 ,,
Acetate, as above, 2·58 g.	$H·CO_2H$ (100 c.c.)	17	+4·51	$1·0 \times 10^{-4}$	$0·9 \times 10^{-4}$	74 mins.
(+)-Formate, 1·30 g.	$H·CO_2H$ (100 c.c.)	21	+2·24	$1·3 \times 10^{-3}$	$1·2 \times 10^{-3}$	57 ,,
(−)-Hydrogen phthalate, 4·04 g.	AcOH (80 c.c.) + H_2O (20 c.c.)	100	−3·23	—	$2·5 \times 10^{-5}$	46 hrs.
(−)-Hydrogen phthalate, 4·11 g.	AcOH (20 c.c.) + NO_2Me (80 c.c.)	100	−2·41	$3·6 \times 10^{-6}$	$3·6 \times 10^{-6}$	320 hrs.

of formate) then falls to zero (solvolysis of formate). The log α–time plot gave two straight lines from which k's for the two stages were calculated.

α-*Naphthylphenylcarbinol* (experiments by Dr. R. E. DABBY).—The carbinol (Acree, *Ber.*, 1904, **37**, 2757) yielded a *hydrogen phthalate*, needles, m. p. 158° (Found: equiv., 384. $C_{25}H_{18}O_4$ requires equiv., 382), and a *hydrogen succinate*, short needles, m. p. 122° (Found: equiv., 338. $C_{21}H_{18}O_4$ requires equiv., 334), by the usual methods. The carbinol on reaction with acetyl chloride or acetic anhydride in presence of pyridine gave the *acetate*, needles, m. p. 80° (Found: C, 82·5; H, 5·9. $C_{19}H_{16}O_2$ requires C, 81·9; H, 6·0%). When heated at 150° for 35 hours it was converted into *di*-(α-*naphthylphenylcarbinyl*) *ether*, which was isolated, by extraction with ethyl ether, concentration, and dilution with benzene, as glistening needles, m. p. 172—173° (Found: C, 90·0; H, 5·7. $C_{34}H_{26}O$ requires C,

90·1; H, 5·8%). From a solution of the hydrogen phthalate (4·0 g.) and sodium toluene-*p*-sulphinate (2·2 g.) in formic acid (50 c.c.), heated under reflux for 8 hours, and then diluted with water, a solid separated which was washed with water and recrystallised from ethyl alcohol, yielding *α-naphthylphenylcarbinyl p-tolyl sulphone* (3·3 g.), plates, m. p. 122° (Found: S, 8·3. $C_{24}H_{20}O_2S$ requires S, 8·5%). From a solution of the hydrogen phthalate (5·0 g.) in ethyl alcohol (75 c.c.), heated under reflux for 18 hours and then concentrated, diluted with ether, and extracted with aqueous ammonia (to remove unchanged phthalate), an ethereal solution of *ethyl α-naphthylphenylcarbinyl ether* was obtained, which was dried and concentrated, yielding the ether, b. p. 203°/14 mm., short needles, m. p. 47° (Found: C, 87·2; H, 7·1. $C_{19}H_{18}O$ requires C, 87·0; H, 6·9%).

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83. *Alkyl–Oxygen Fission in Carboxylic Esters. Part VII. Hydrolysis of Methyl-β-naphthylcarbinyl Hydrogen Phthalate.*

By M. P. BALFE, J. KENYON, and C. E. SEARLE.

The hydrolysis of the hydrogen phthalate in a variety of alkaline solutions confirms that the racemising mechanism (probably unimolecular) occurs in low concentrations of alkali, and at higher concentrations of alkali is suppressed by the mechanism (probably bimolecular) which results in retention of optical activity.

Ethers of methyl-β-naphthylcarbinol are described, and the *p*-tolyl sulphones of methyl-α- and -β-naphthylcarbinols. Reduction of methyl β-naphthyl ketone by zinc in alkaline solution gives the corresponding glycol, which readily undergoes the pinacone rearrangement.

IN previous communications in this series (*J.*, 1942, 556, 605; 1945, 797, 803, 807), the observations of the effect of strength of alkali on the rotatory powers of carbinols with electron-releasing substituents, obtained by hydrolysis of their hydrogen phthalates, have been confined to experiments with "strong alkali" (*e.g.*, excess of 10N-sodium hydroxide) and "weak alkali" (*e.g.*, sodium carbonate or sodium hydroxide in small excess). We have thought it of interest to examine the effect of intermediate alkalinities, and have used (+)-methyl-β-naphthylcarbinyl hydrogen phthalate as substrate. During the hydrolysis, the alkalinity of the solution necessarily decreases, and it is undesirable to counteract this by the use of buffered solutions, since the anions thus introduced might divert a part of the reaction. To keep the decrease of alkalinity as small as possible, we have used as low a concentration of hydrogen phthalate as is consistent with isolation of the liberated carbinol; the table gives

Hydrolysis of optically active hydrogen phthalates
(at 90° unless otherwise stated).

Hydrogen phthalate of:		Alkali.		OH′ activity.†		Racemisation, %, of liberated carbinol.
	*c.**		*c.**	Initial.	Final.	
Methyl-β-naphthylcarbinol	0·62	NaOH	2·50	2500 ‡	—	nil
,, ,,	0·025	,,	0·50	339	302	3
,, ,,	0·079	Na_3PO_4	0·67	76	7·9	4
,, ,,	0·031	NH_4OH §	19·6	11·2	1·3	2
,, ,,	0·021	Na_2CO_3	0·28	3·3	0·35	19
,, ,,	0·21	,,	0·09	0·66	0·12	43
,, ,,	0·083	,, ‖	0·05	0·22	0·07	48
2-Octyl alcohol	0·055	Na_3PO_4	0·73	43·7	5·5	nil
,, ,, ...	0·024	Na_2CO_3	0·28	3·2	0·4	nil

* Moles/litre. † Millimoles/litre.
‡ Calc. from *c*, an activity coefficient of 1·0 being assumed.
§ At 20°, hydrolysis not completed. ‖ At 100°.

the percentage of racemisation observed in carbinols formed by hydrolysis of the hydrogen phthalates in a variety of alkaline solutions, the initial and final alkalinities (hydroxyl-ion

activities) of which are recorded. The increase in racemisation, with decreasing alkalinity of solution, is clearly illustrated, and a plot of percentage racemisation against mean alkalinity gives a fairly smooth curve. On the other hand, no racemisation occurs during the hydrolysis of (+)-2-octyl hydrogen phthalate in solutions which produce nearly 50% racemisation in the hydrolysis of the methyl-β-naphthylcarbinyl ester.

Methyl and ethyl methyl-β-naphthylcarbinyl ethers are formed when the (±)-hydrogen phthalate is heated with the appropriate alcohol, and di(methyl-β-naphthylcarbinyl) ether is formed on heating the carbinol at 200°. *p*-Tolyl sulphones are formed on warming methyl-α- and -β-naphthylcarbinyl hydrogen phthalates with sodium toluene-*p*-sulphinate in formic acid.

Aluminium *iso*propoxide is the best reducing agent for preparation of methyl-β-naphthylcarbinol from the ketone. Sodium amalgam gives a higher proportion of by-products, and zinc with alcoholic sodium hydroxide gives only 1 : 2-dimethyl-1 : 2-di-β-naphthylethylene glycol, which when heated in acetic anhydride undergoes the pinacol–pinacone transformation.

Experimental.

(−)-Methyl-β-naphthylcarbinyl hydrogen phthalate, prepared as described by Collyer and Kenyon (*J.*, 1940, 676), had m. p. 91—93°, $[\alpha]_D^{17}$ −49·9° in ethyl alcohol (*c*, 2·5). The (+)-2-octyl ester was prepared as described by Kenyon (*Org. Synth.*, Coll. Vol. I, 410).

Hydrolysis.—Solutions of the hydrogen phthalate (3-g. portions) in the appropriate alkali (see table) were heated, mostly at 90° (table). The carbinols separated as oils, and heating was continued for 2 hours after this separation ceased (total times ranged between 2 and 4 hours). pH values of initial and final solutions were measured with the " Alki " electrode on a Cambridge pH meter at 20°, and hydroxyl-ion activities were calculated from the appropriate value of K_w. The liberated carbinols were isolated in approximately theoretical yield by extraction of the final solution with ether; which extracts were then dried (K_2CO_3) and freed from solvent. The carbinols were converted into hydrogen phthalates by the usual method, and these esters extracted from ethereal solution with aqueous sodium carbonate, precipitated with hydrochloric acid, washed, and dried ($CaCl_2$). The % racemisation in the table is the rotatory power of the recovered phthalate as a percentage of that of the original phthalate. Recrystallisation of the recovered phthalate was not permissible since it might effect optical enrichment.

Methyl-β-naphthylcarbinyl Ethers.—The (±)-hydrogen phthalate (4 g.) was heated under reflux in 75% aqueous ethyl alcohol (60 c.c.) for 60 hours. The mixture was then diluted with water and extracted with ether. The extract was washed with sodium carbonate solution, dried (Na_2SO_4), and concentrated. Distillation of the residual oil (2·6 g.) yielded the *ethyl ether*, b. p. 145—148°/16 mm., n_D^{16} 1·5743 (Found : C, 84·1; H, 8·4. $C_{14}H_{16}O$ requires C, 84·0; H, 8·0%). The *methyl ether*, prepared similarly by use of aqueous methyl alcohol, had b. p. 148—151°/18 mm., n_D^{16} 1·5829 (Found : C, 83·7; H, 7·6. $C_{13}H_{14}O$ requires C, 83·9; H, 7·5%). *Di(methyl-β-naphthylcarbinyl) ether* was formed on heating the carbinol at 200° for 3 hours. A little carbinol was distilled from the product, and the residue, on redistillation, gave the ether, b. p. 240—245°/14 mm. (Found : C, 88·0; H, 6·7. $C_{24}H_{22}O$ requires C, 88·3; H, 6·7%).

Methyl-α- and -β-naphthylcarbinyl p-*Tolyl Sulphones.*—The hydrogen phthalate (2·0 g.) of the α-carbinol (*J.*, 1946, 797) and of the β-carbinol were separately heated at 90° with sodium toluene-*p*-sulphinate (1·3 g.) in formic acid (25 c.c.), then diluted with water, and the precipitates recrystallised from ethyl alcohol. The *sulphone* of the α-carbinol had m. p. 144·5° (Found : S, 10·5%); that of the β-carbinol had m. p. 153—154° (Found : S, 10·2. $C_{18}H_{18}O_2S$ requires S, 10·3%).

Reduction of Methyl β-Naphthyl Ketone.—With aluminium iso*propoxide.* See Collyer and Kenyon (*loc. cit.*).

With zinc and alcoholic alkali. The ketone (10 g.), zinc dust (10 g.), and sodium hydroxide (10 g.) were heated under reflux in ethyl alcohol (100 c.c.) for 5 hours. The mixture was filtered and diluted with water, and the precipitate recrystallised from ethyl alcohol, yielding 1 : 2-*dimethyl*-1 : 2-*di*-β-*naphthylethylene glycol*, m. p. 184° [Found, after heating at 110°/20 mm. over P_2O_5 for 1 hour : C, 83·9; H, 6·2%; *M* (Rast), 310. $C_{24}H_{22}O_2$ requires C, 84·2; H, 6·4%; *M*, 342]. The glycol was heated under reflux in acetic anhydride for 1½ hours, and the mixture diluted with water; the precipitate, recrystallised from aqueous ethyl alcohol, yielded a *compound*, m. p. 144—145° (Found : C, 88·5; H, 6·4. $C_{24}H_{20}O$ requires C, 88·9; H, 6·2%), probably the pinacone (or mixture of the two possible pinacones), since it gave a precipitate (difficult to purify) with 2 : 4-dinitrophenylhydrazine.

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84. *Alkyl–Oxygen Fission in Carboxylic Esters. Part VIII. Esters of* p-*Methylthio- and* p-*Methylsulphonyl-diphenylcarbinols.*

By M. P. Balfe, R. E. Dabby, and J. Kenyon.

The (−)-hydrogen phthalate of *p*-methylthiodiphenylcarbinol yields, by methods previously described, a half-racemised neutral dicarbinyl phthalate and the racemic *p*-tolyl sulphone. It reacts with acetic acid to yield the (±)-acetate, with concurrent racemisation of the unreacted phthalate, and on hydrolysis with aqueous alkali yields a partly racemised carbinol; optically pure (−)-carbinol is obtained on hydrolysis of the (−)-hydrogen phthalate in alcoholic alkali. These reactions are characteristic of the unimolecular mechanism of alkyl–oxygen fission. Oxidation of the *p*-methylthio- to the *p*-methylsulphonyl derivative introduces an electron-attracting *p*-substituent in place of the electron-releasing methylthio-group, and the (+)-hydrogen phthalate of *p*-methylsulphonyldiphenylcarbinol accordingly does not undergo reactions involving alkyl–oxygen fission.

Reductions of *p*-methylthiobenzophenone under acid or alkaline conditions and of *p*-methylsulphonylbenzophenone under acid conditions yield the corresponding *p*-substituted diphenylcarbinols, but when *p*-methylsulphonylbenzophenone is reduced under alkaline conditions, the methylsulphonyl group is removed and unsubstituted diphenylcarbinol is produced.

(−)-*p*-Methylthiodiphenylcarbinol and certain of its derivatives undergo reactions involving alkyl–oxygen fission similar to those of derivatives of methoxyphenyl-phenyl- and -α-naphthyl-carbinol, described and discussed in Parts II (*J.*, 1942, 605) and IV (*J.*, 1946, 803). The (−)-hydrogen phthalate yields the (−)-carbinol on hydrolysis with alcoholic alkali, and extensively racemised (−)-carbinol on hydrolysis in aqueous alkali; it also yields the (±)-carbinol on hydrolysis by sulphuric acid in acetone solution. From a solution of the (−)-hydrogen phthalate in an equimolecular proportion of aqueous sodium hydroxide, the neutral ester, di-(*p*-methylthiophenyl)carbinyl phthalate, separates, and from this on hydrolysis with alcoholic alkali the carbinol is obtained with half the rotatory power of that obtained from the hydrogen phthalate. The (−)-hydrogen phthalate, dissolved in an equimolecular proportion of aqueous sodium toluene-*p*-sulphinate to yield the (±)-*p*-tolyl sulphone. It yields the (±)-chloride (chloro-*p*-methylthiodiphenylmethane) on reaction with acetyl chloride. The (−)-carbinol reacts with acetyl chloride in presence of pyridine to yield the (−)-acetate, and in the absence of pyridine to yield the (±)-chloride. The chloride is also obtained by triturating the carbinol, and a number of its derivatives, with concentrated hydrochloric acid; these reactions are accompanied by complete racemisation.

Solutions of (−)-*p*-methylthiodiphenylcarbinyl hydrogen phthalate in acetic acid undergo racemisation at 100° ($t_{\frac{1}{2}}$ = 14 minutes) and at room temperature ($t_{\frac{1}{2}}$ = 100 hours) with formation of the (±)-acetate and concurrent racemisation of the unreacted fraction of the phthalate. Solutions in ethyl alcohol react similarly at 100°, yielding the (±)-ethyl ether. Solutions of the carbinol in acetic acid also yield the (±)-acetate at 100° ($t_{\frac{1}{2}}$ = 2 hours) and undergo a very slow racemisation at room temperature.

(+)-*p*-Methylsulphonyldiphenylcarbinol is obtained by oxidation of (−)-*p*-methylthiodiphenylcarbinol with hydrogen peroxide. It yields a (+)-hydrogen phthalate identical with that obtained by oxidation of (−)-*p*-methylthiodiphenylcarbinyl hydrogen phthalate. Hydrolysis of this (+)-phthalate with aqueous alkali yields (+)-*p*-methylsulphonyldiphenylcarbinol without any racemisation. (±)-*p*-Methylsulphonyldiphenylcarbinyl hydrogen phthalate does not yield the neutral dicarbinyl phthalate, nor does it react with sodium toluene-*p*-sulphinate, when dissolved in an equimolecular proportion of aqueous sodium hydroxide. These observations illustrate how the electron-releasing tendency of the *p*-methylthio-group, which promotes alkyl–oxygen fission in derivatives of *p*-methylthiodiphenylcarbinol, is converted into an electron-attracting tendency when the methylthio-group is oxidised to the sulphone. The same effect is illustrated by the inertness of *p*-bromomethylsulphonylbenzene towards magnesium, whereas *p*-bromomethylthiobenzene readily forms the Grignard reagent.

When reduced in acid conditions (zinc and acetic acid), both *p*-methylthio- and *p*-methylsulphonyl-benzophenone yield the corresponding diphenylcarbinols. Under alkaline conditions (zinc dust and sodium hydroxide, or sodium amalgam), *p*-methylthiobenzophenone yields

p-methylthiodiphenylcarbinol, but *p*-methylsulphonylbenzophenone yields diphenylcarbinol, with fission of the bond between the sulphur atom and the aromatic nucleus. Electron-accession to this carbon–sulphur bond is assisted by the *p*-carbonyl group, but reduction can only occur if this accession is followed either by addition of protons to the resulting anionic sites, which is impossible in the present examples, or by fission of the bond joining these sites. Presumably the fact that this fission occurs only with the *p*-methylsulphonyl derivative and under alkaline conditions, is related to the comparative stability of the methylsulphinate anion (cf. Birch, *Faraday Soc. Discussions*, 1947, **2**, 247).

Experimental.

Thioanisole, prepared by the action of methyl sulphate on sodium thiophenoxide in aqueous solution (yield 91%), had b. p. 82°/18 mm.; d_4^{20} 1·053; n_D^{20} 1·5835. *p*-Bromothioanisole, prepared by the action of bromine on a solution of thioanisole in carbon disulphide, separates from methanol in glistening plates, m. p. 37·5° (yield 92%).

p-*Methylthiobenzophenone*.—Powdered aluminium chloride (112 g.) was added during 45 minutes to a mechanically stirred mixture of thioanisole (93 g.), benzoyl chloride (87 c.c.), and carbon disulphide (300 c.c.); the temperature of the reaction mixture was kept below 20° during the mixing, and subsequently raised to 40—45° for an hour. The solid product was filtered off, washed with carbon disulphide, and decomposed with hydrochloric acid, decomposition being completed by heating on the steam-bath. When the hot reaction mixture was poured on crushed ice, the ketone set to a crystalline mass which, after being washed with sodium hydroxide and dried, weighed 153 g. and had m. p. 75—76°. p-*Methylthiobenzophenone* separates from ether–light petroleum in rhombs, or from methanol in prismatic needles, m. p. 78°. It distils unchanged, b. p. 221°/11 mm. (Found: C, 73·3; H, 5·4; S, 13·4. $C_{14}H_{12}OS$ requires C, 73·6; H, 5·3; S, 14·0%).

p-*Methylthiodiphenylcarbinol*—(*a*) Zinc dust (46 g.) was added to a solution of *p*-methylthiobenzophenone (46 g.) and sodium hydroxide (46 g.) in ethyl alcohol (300 c.c.), and the mixture heated under reflux for 5—6 hours, and filtered whilst hot; the residue was washed with boiling alcohol (30 c.c.), and the filtrate diluted with water, p-*methylthiodiphenylcarbinol*, m. p. 92—93° (46 g.), being obtained. It separates from ether–light petroleum in silky needles, m. p. 94° (96%) (Found: C, 72·8; H, 6·2; S, 14·0. $C_{14}H_{14}OS$ requires C, 73·0; H, 6·1; S, 14·1%). A parallel result was obtained by the action of sodium amalgam on an alcoholic solution of the ketone.

(*b*) Benzaldehyde (1·0 g.) in ethereal solution was added to a Grignard reagent prepared from *p*-bromothioanisole (2·1 g.); the resulting methylthiodiphenylcarbinol (yield 45%) had m. p. 94° alone or when mixed with the carbinol from method (*a*). Methylthiodiphenylcarbinol, after being heated at 145° for an hour, was recovered unchanged. It does not react with methyl iodide.

(±)-*Methylthiodiphenylcarbinyl Hydrogen Phthalate*.—To a solution of phthalic anhydride (37 g.) in pyridine (40 g.), the carbinol (57·5 g.) was added, and the mixture—which became homogeneous in 15 minutes—was kept at 50—60° for 3 hours. The viscous product was dissolved in acetone (150 c.c.), and the solution decomposed by the addition of hydrochloric acid (100 c.c.) diluted with water (2 l.). The precipitated oily material soon set to a crystalline solid, m. p. 118—120°. The *hydrogen phthalate* separates from benzene–light petroleum or carbon disulphide in hemispherical clusters of needles, m. p. 123—124° (90%) (Found, by titration with 0·1N-NaOH: *M*, 378. $C_{22}H_{18}O_4S$ requires *M*, 378). When a solution of the acid ester (0·500 g.) in alcoholic potash was heated under reflux for 30 minutes, 30·28 c.c. were neutralised (Calc.: 30·32 c.c.), whence *M* = 378; the neutralised solution of the hydrolysed ester yielded the carbinol (0·300 g. Calc., 0·304 g.), m. p. 94°.

(−)-*Methylthiodiphenylcarbinyl Hydrogen Phthalate*.—A solution of the (±)-acid ester (95 g.) and quinine (95 g.) in warm alcohol (200 c.c.; 96%) after being kept overnight deposited the crystalline quinine salt; this after three crystallisations from the same solvent yielded optically pure quinine (−)-methylthiodiphenylcarbinyl phthalate (40 g.) as glistening needles, m. p. 116—117°. Decomposition of this in acetone solution with hydrochloric acid yielded the (−)-acid ester (19·5 g.), which separates from carbon disulphide in fibrous needles, m. p. 96—97°. Rotatory powers are given in the table.

Specific rotatory powers of (−)-methylthiodiphenylcarbinyl hydrogen phthalate.

Solvent	g./100 c.c. of soln.	*t*.	$[\alpha]_{4358}$	$[\alpha]_{5893}$	$[\alpha]_{5780}$	$[\alpha]_{5461}$	$[\alpha]_{5086}$	$[\alpha]_{4900}$	$[\alpha]_{4358}$
CS_2	2·501	18°	−25·0°	−30·6°	−31·6°	−33·4°	−45·0°	−53·0°	−75·0°
C_6H_6	5·002	19	−21·3	−22·0	−24·0	−27·5	−34·3	−44·3	−56·0
$COMe_2$	4·998	19	−9·0	−10·0	−10·9	−15·2	−16·5	−17·5	−27·5
$CHCl_3$	5·011	18·5	−9·0	−9·6	−11·4	−13·4	−15·0	−20·0	−27·4
MeOH	5·003	15	−8·0	−9·5	−11·0	−13·5	−16·0	−18·5	−25·0
MeOAc	5·013	18	−6·5	−7·1	−7·4	−8·0	−10·0	−13·0	−17·5

(−)-*Methylthiodiphenylcarbinol*.—The (−)-acid ester (2 g.) was dissolved in a solution of sodium ethoxide [from sodium (0·5 g.) in absolute alcohol (20 c.c.)], and the whole heated gently for a few minutes. On dilution with water the (−)-*carbinol* separated as a crystalline solid, and recrystallised from carbon disulphide in clusters of short needles (1·0 g.), m. p. 56—57°, $[\alpha]_D^{20}$ −13·5° (*l*, 2; *c*, 6·000 in carbon disulphide). Reconversion of this carbinol into its hydrogen phthalate yielded a product possessing a rotatory power almost identical with that of the original acid ester, indicating absence of racemisation.

When, however, aqueous sodium hydroxide of high or low concentration is used to effect the hydrolysis the liberated alcohol is extensively racemised.

Acetate. To a solution of the carbinol (2·3 g.; $[\alpha]_D$ −8·6° in carbon disulphide) in pyridine (2 g.) was added acetic anhydride (1·1 g.)—or acetyl chloride (0·8 g.)—and the mixture gently warmed for a few minutes. The resulting (−)-*acetate* (1·9 g.) had b. p. 221°/15 mm., d_4^{21} 1·144, n_D^{20} 1·5912, $[\alpha]_D^{20}$ −29·4° (*l*, 2; *c*, 3·756 in carbon disulphide) [Found: C, 70·3; H, 6·2%; *M*, 272 (by hydrolysis). $C_{16}H_{14}O_2S$ requires C, 70·6; H, 5·9%; *M*, 272].

The (±)-*acetate* was obtained when the (−)-carbinol (1 g.) was heated with glacial acetic acid (15 c.c.) for several hours on the steam-bath. It had b. p. 221°/15 mm., n_D^{20} 1·5912 [Found: *M*, 273 (by hydrolysis)].

Reactions of (−)-*Methylthiodiphenylcarbinyl Hydrogen Phthalate.*—(i) *Formation of di(methylthiodiphenylcarbinyl) phthalate.* (*a*) A solution of the (−)-hydrogen phthalate (3 g.; $[\alpha]_D$ −27·0° in carbon disulphide) in sodium hydroxide (27 c.c.; 0·3N.) after some 40 minutes began to deposit the neutral *phthalate*; this, after 3 days, was removed as a glassy mass (2·1 g.; calc., 2·3 g.), m. p. 40—45°, which could not be obtained crystalline. It had $[\alpha]_D$ −23·6° in carbon disulphide (*c*, 2·501; *l*, 2) [Found: *M*, 596 (by hydrolysis). $C_{34}H_{30}O_4S_2$ requires *M*, 590]. By hydrolysis with potassium hydroxide in absolute alcohol the neutral ester yielded (−)-methylthiodiphenylcarbinol, m. p. 90—91°, $[\alpha]_D$ −4·4° in carbon disulphide. Hydrolysis of the original (−)-hydrogen phthalate under similar conditions yielded a (−)-carbinol of approximately twice the rotatory power, *i.e.*, $[\alpha]_D$ −8·6°, and m. p. 56—57°.

(*b*) A solution of the (±)-hydrogen phthalate (3·78 g.) in chloroform (25 c.c.) after being heated under reflux for 5 hours had deposited phthalic acid (0·55 g.). From the filtrate there were isolated unchanged acid ester (1·5 g.) and the neutral phthalate (1·5 g.) (Found, by hydrolysis; *M*, 594).

(ii) *Formation of methylthiodiphenylcarbinyl* p-*tolyl sulphone.* A solution of the (−)-hydrogen phthalate (0·5 g.; $[\alpha]_D$ −17·0°) in sodium hydroxide (4·5 c.c.; 0·3N.) was rapidly filtered into a solution of sodium toluene-*p*-sulphinate (0·28 g.) in water (5 c.c.). Separation of the crystalline *sulphone* began after some 30 minutes and was complete within 24 hours. The sulphone (0·25 g.) was optically inactive and separated from methanol in needles, m. p. 172° alone and when mixed with sulphone prepared in a similar manner from the (±)-hydrogen phthalate (Found: S, 16·9. $C_{31}H_{30}O_2S_2$ requires S, 17·3%).

(iii) *Formation of ethyl* (±)-*methylthiodiphenylcarbinyl ether.* A solution of the (−)-hydrogen phthalate (4 g.; $[\alpha]_D$ −30·6° in carbon disulphide) in absolute alcohol (70 c.c.) was heated under reflux for 45 minutes; the mixture yielded the (−)-hydrogen phthalate (1·4 g.), the rotatory power of which had fallen to $[\alpha]_D$ −22·4°, and the (±)-*ethyl ether* (1·7 g.), b. p. 206—208°/15 mm., n_D^{20} 1·5910, d_4^{21} 1·0891 (Found: C, 74·2; H, 7·3. $C_{16}H_{18}OS$ requires C, 74·4; H, 7·0%). When the heating was prolonged to 4 hours the (−)-ester was converted completely into the (±)-ether.

(iv) *Formation of* (±)-*methylthiodiphenylcarbinyl acetate.* A solution of the (−)-hydrogen phthalate (1 g.; $[\alpha]_D$ −30·6°) in glacial acetic acid (20 c.c.) when kept for an hour at room temperature yielded (−)-hydrogen phthalate (0·45 g.) with $[\alpha]_D$ −21·8° and (±)-methylthiodiphenylcarbinyl acetate (0·36 g.), b. p. 216°/14 mm., n_D^{20} 1·5912.

(v) *Hydrolysis with sulphuric acid.* The (−)-hydrogen phthalate (1 g.; $[\alpha]_D$ 20° −30·6° in carbon disulphide) was heated under reflux for 3 hours in acetone (15 c.c.) containing sulphuric acid (0·5 c.c.) and water (4 c.c.). (±)-Carbinol (0·5 g.), m. p. and mixed m. p. 94°, was formed [the neutral (−)-dicarbinyl phthalate yielded (±)-carbinol in a similar experiment]. From a similar solution of the (−)-hydrogen phthalate in acetone and sulphuric acid, after 2 days at room temperature, 0·75 g. of hydrogen phthalate with $[\alpha]_D^{20}$ −24·8° (in carbon disulphide) was extracted by sodium carbonate, and the residue yielded ±)-carbinol (0·1 g.; m. p. 94°).

Preparation of Methylthiodiphenylcarbinyl Chloride.—From the carbinol. (i) By use of concentrated hydrochloric acid. The (−)-carbinol (2 g.) when triturated with the acid (40 c.c.) gradually changed to a liquid which, in turn, solidified. The resulting (±)-*methylthiodiphenylcarbinyl chloride* separated from light petroleum and a little ether in needles, m. p. 56° (Found: Cl, 14·1. $C_{14}H_{13}SCl$ requires Cl, 14·2%). (ii) By use of acetyl chloride. The (−)-carbinol (1 g.) dissolved readily in acetyl chloride (1 g.) and yielded the (±)-chloride, m. p. 56°.

From esters. The optically active acetate, hydrogen phthalate, and neutral phthalate of methylthiodiphenylcarbinol when triturated with concentrated hydrochloric acid at room temperature yielded, in each case, (±)-methylthiodiphenylcarbinyl chloride, m. p. 56°. The (+)-hydrogen phthalate (1·9 g.) on reaction with acetyl chloride (0·7 c.c.) yielded (±)-chloride (1·2 g.), m. p. and mixed m. p 56°.

Reactions of Methylthiodiphenylcarbinyl Chloride.—(i) With water, this gave the carbinol, m. p. 94°, and (ii) with absolute alcohol the ethyl ether, b. p. 212°/20 mm., n_D^{20} 1·5910. (iii) With sodium benzoate it yielded the *benzoate*, hemispherical clusters of needles, m. p. 59° alone and mixed with a specimen prepared directly from the carbinol (Found: C, 75·6; H, 5·5. $C_{21}H_{18}O_2S$ requires C, 75·45; H, 5·4%). (iv) With sodium toluene-*p*-sulphinate it afforded the sulphone, m. p. 172°, and (v) with potassium hydrogen phthalate the hydrogen phthalate (m. p. and mixed m. p. 123—124°) together with a small proportion of carbinol (m. p. 94°).

(±)-p-*Methylsulphonyldiphenylcarbinol*—(*a*) A mixture of methylthiodiphenylcarbinol (1 g.), glacial acetic acid (20 c.c.), and hydrogen peroxide (3·3 c.c.; 90-vol.) after being kept for 2 days at room temperature was mixed with an excess of dilute sodium hydroxide solution. The precipitated p-*methylsulphonyldiphenylcarbinol* separated from hot water or methanol in glistening plates (1 g.), m. p. 125—125·5° (Found: C, 64·0; H, 5·5; S, 12·2. $C_{14}H_{14}O_3S$ requires C, 64·1; H, 5·3; S, 12·2%).

(*b*) A mixture of methylthiobenzophenone (2 g.) in acetic acid (25 c.c.) and potassium permanganate (2·2 g.), after being heated on the steam-bath for 40 minutes, was decolorised with sulphur dioxide and diluted with water. The precipitated *p-methylsulphonylbenzophenone* separated from alcohol in glistening plates (2·1 g.), m. p. 141° (Found: S, 11·8. $C_{14}H_{12}O_3S$ requires S, 12·3%). When the permanganate was replaced by hydrogen peroxide a similar result was obtained. This ketone (4 g.) on reduction with aluminium (0·5 g.) and anhydrous *iso*propyl alcohol (30 c.c.) during 2 hours yielded *p*-methylsulphonyldiphenylcarbinol, glistening plates (3·7 g.) (from ethanol), m. p. 125—125·5° alone and when mixed with the product from (*a*) or with the product obtained when the ketone was reduced with zinc dust and acetic acid.

Reduction of p-*Methylsulphonylbenzophenone to Diphenylcarbinol.*—A mixture of the ketone (4 g.), ethyl alcohol (150 c.c.), and sodium amalgam (80 g. of 5%) was heated under reflux for 2 hours, and the alcoholic solution diluted with water. The resulting crystalline material, which was sulphur-free, separated from ether–light petroleum in long, silky needles, m. p. 66—67° alone or when mixed with an authentic specimen of diphenylcarbinol. A similar result was obtained when a mixture of the ketone (1 g.), ethanol (30 c.c.), sodium hydroxide (5 g.), and zinc dust (5 g.) was left overnight at room temperature.

Oxidation of (−)-*Methylthiodiphenylcarbinol to* (+)-p-*Methylsulphonyldiphenylcarbinol.*—A solution of (−)-methylthiodiphenylcarbinol (3·6 g.; $[\alpha]_D$ −4·5° in methylene chloride) in glacial acetic acid (75 c.c.) and hydrogen peroxide (15 c.c.; 90-vol.) after being kept for 6 days and dilution with dilute sodium hydroxide deposited (+)-p-*methylsulphonyldiphenylcarbinol*, which separated from methylene chloride in glistening plates (3·0 g.), m. p. 146—147°, $[\alpha]_D^{19}$ +45·1° (*l*, 2; *c*, 5·025 in methylene chloride).

(+)-*Methylsulphonyldiphenylcarbinyl Hydrogen Phthalate.*—(*a*) A mixture of the (+)-carbinol (1·5 g.), phthalic anhydride (0·84 g.), and pyridine (1 g.) was heated on the steam-bath for 2 hours and worked up in the usual way. The resulting *hydrogen phthalate* separated from methylene chloride–ligroin in plates (2·1 g.), m. p. 105—107°, $[\alpha]_D^{19}$ +37·0° (*l*, 2; *c*, 5·113 in methylene chloride) (Found, by titration: *M*, 415. $C_{32}H_{14}O_6S$ requires *M*, 410).

(*b*) *By oxidation of* (−)-*methylthiodiphenylcarbinyl hydrogen phthalate.* A solution of the (−)-ester (3 g.; $[\alpha]_D$ −22·5° in carbon disulphide solution) in glacial acetic acid (30 c.c.) and hydrogen peroxide (10 c.c.) was kept for 3 days and diluted with water. The precipitated sulphonyl ester separated from methylene chloride–ligroin in plates (2·9 g.), m. p. 106—108°, $[\alpha]_D^{19}$ +36·6° in methylene chloride. By hydrolysis with sodium hydroxide it yielded (+)-*p*-methylsulphonyldiphenylcarbinol, $[\alpha]_D^{19}$ +44·8° in methylene chloride.

Hydrolysis of (+)-p-*Methylsulphonyldiphenylcarbinyl Hydrogen Phthalate.*—(a) *In anhydrous alcohol.* The (+)-ester (0·5 g.), heated with an alcoholic solution of sodium ethoxide, yielded (+)-*p*-methylsulphonyldiphenylcarbinol, which separated from methylene chloride in glistening plates (0·25 g.), m. p. 146—147°, $[\alpha]_D^{19}$ +45·0° (*l*, 2; *c*, 2·203 in methylene chloride).

(b) *In aqueous solution.* The (+)-ester (0·5 g.) in sodium hydroxide (15 c.c. of 0·3N.), heated on the steam-bath for 30 minutes, yielded the (+)-carbinol (0·3 g.), m. p. 146—147°, $[\alpha]_D^{19}$ +44·8° (*l*, 2; *c*, 2·221 in methylene chloride).

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85. *Alkyl–Oxygen Fission in Carboxylic Esters. Part IX. Methyl-2-thienylcarbinol.*

By I. G. ANDERSON, M. P. BALFE, and J. KENYON.

Optically impure di(methyl-2-thienylcarbinyl) phthalate and methyl-2-thienylcarbinyl *p*-tolyl sulphone are prepared.

BY the methods described in Parts II (*J.*, 1942, 605), IV (*J.*, 1946, 803), and V (*J.*, 1946, 807), optically impure di(methyl-2-thienylcarbinyl) phthalate and methyl-2-thienylcarbinyl *p*-tolyl sulphone have been prepared from the hydrogen phthalate: the latter reaction is accompanied by racemisation. The neutral phthalate is obtained in 20%, and the sulphone in 30% yield; from substituted diphenylcarbinols (*loc. cit.*), yields of approximately 100% are obtained. Anderson, Balfe, and Kenyon (*J.*, 1950, 1866) have shown that when the hydrogen phthalate is hydrolysed in 0·4N-alcoholic alkali containing 1% of water, the resulting methyl-2-thienylcarbinol is 97% optically pure. Hydrolysis by approximately 10N-aqueous alkali gives a carbinol which is 88% optically pure. *p*-Methoxyphenyl-α-naphthylcarbinol (Part IV, *loc. cit.*) is about 50% racemised when prepared by hydrolysis of its hydrogen phthalate with 10N-aqueous alkali. It therefore appears that the tendency to alkyl–oxygen fission in the ester of methyl-2-thienylcarbinol is less than in the esters of substituted diphenyl-

carbinols, but greater than in the esters of substituted allyl alcohols (Part I, *J.*, 1942, 556) which yield neither the neutral ester nor the sulphone by the methods now under discussion.

Experimental.

The preparation of (+)- and (−)-methyl-2-thienylcarbinol is described by Anderson, Balfe, and Kenyon (*loc. cit.*).

Di(methyl-2-thienylcarbinyl) Phthalate.—The oil which separated during 12 hours from a solution of the (+)-hydrogen phthalate (5 g.) and sodium hydroxide (0·18 g.) in water (100 c.c.) was dissolved in ether, and the solution dried and concentrated. Methyl-2-thienylcarbinol (1·5 g.; b. p. 99°/18 mm.; n_D^{20} 1·5413) was distilled from the residue, leaving the crude neutral *phthalate* as a gum (0·7 g.) (Found, by hydrolysis with boiling alcoholic potassium hydroxide: equiv., 203. $C_{26}H_{18}O_4S_2$ requires equiv., 193); it could not be crystallised. The aqueous residue was acidified and filtered, evaporated to dryness, and extracted with ethyl alcohol; a combined yield of 2·6 g. of phthalic acid, m. p. 198° (decomp.), was obtained.

Methyl-2-thienylcarbinyl p-*Tolyl Sulphone.*—A filtered solution of the (−)-hydrogen phthalate (2 g.; $[\alpha]_D^{20}$ −10·0° in benzene) in 0·5N-aqueous sodium hydroxide (20 c.c.) was quickly mixed with a solution of sodium toluene-*p*-sulphinate (1·5 g.) in water (25 c.c.). After 24 hours the crystalline deposit (0·6 g.) was separated and recrystallised from ethyl alcohol, yielding the crude *sulphone*, m. p. 89—91° (Found: C, 58·4; H, 5·0; S, 22·2. $C_{13}H_{14}O_2S_2$ requires C, 58·6; H, 5·3; S, 24·2%), which was optically inactive.

Hydrolysis of (−)-*Methyl-2-thienylcarbinyl Hydrogen Phthalate.*—The acid ester (4·3 g.; $[\alpha]_D$ −20·5° in benzene, *i.e.*, 35% of the maximum rotatory power) was dissolved in a very concentrated solution of sodium hydroxide (1·6 g.) through which a current of steam was passed and the volume of the solution kept below about 5 c.c. The recovered alcohol (1·7 g.) had b. p. 89°/10 mm., $[\alpha]_D^{13}$ −7·6° (*l*, 2; *c*, 5·00 in benzene).

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86. *Alkyl–Oxygen Fission in Carboxylic Esters. Part X. Phthalates of Di-*p*-methoxyphenylcarbinol and of* tert.*-Alcohols.*

By M. P. Balfe, J. Kenyon, and E. M. Thain.

Di-*p*-methoxyphenylcarbinol does not react with phthalic anhydride in presence of pyridine. Reaction occurs, however, in the presence of triethylamine, yielding a mixture of the acid and the neutral phthalate. It is suggested that the stronger base overcomes the effect of the two electron-releasing *p*-substituents which hinder the separation of the proton from the hydroxyl group. *tert.*-Alcohols, however, do not react with phthalic anhydride even in the presence of triethylamine.

Evidence is put forward that aralkyl groups are more firmly held in symmetrically substituted neutral phthalates than in other esters.

Di-*p*-methoxyphenylcarbinol does not react with phthalic anhydride in the presence of pyridine at 40° or 100°; nor can its hydrogen phthalate be formed by reaction of the potassium-derivative of the carbinol with phthalic anhydride, or by the reaction (Houben, *Ber.*, 1906, **39**, 1736) of the carbinylmagnesium bromide with phthalic anhydride. The esterification normally involves separation of a proton from the carbinol (Gerrard, *J.*, 1940, 218; Balfe, Kenyon, *et al.*, *J.*, 1942, 605). In view of the presence in the carbinol of two electron-releasing *p*-substituents, it was thought possible that this alcohol could be esterified by an acid-catalysed reaction, involving separation of the hydroxyl ion. However, such reactions yielded only products of the action of acid on the carbinol, *viz.*, bisdi-*p*-methoxyphenylcarbinyl ether, *pp'*-dimethoxybenzophenone, and di-*p*-methoxyphenylmethane. Alternatively, it appeared possible that, since the electron-releasing substituents lessen the ease of removal of the proton (as in the comparison of the dissociation constants of benzoic and anisic acids, Ingold, *J.*, 1933, 1124), the esterification might be promoted by the use of a stronger base than pyridine ($K_b = 2·4 \times 10^{-9}$), by virtue of the greater affinity of the stronger base for the proton. It has in fact been found that in the presence of triethylamine ($K_b = 6·4 \times 10^{-4}$) the esterification proceeds readily, some of the neutral dicarbinyl phthalate being formed along with the acid

ester. Triethylamine also accelerates the formation of the urethane from di-*p*-methoxyphenylcarbinol with phenyl *iso*cyanate.

The hydrogen phthalate of di-*p*-methoxyphenylcarbinol, like that of *p*-methoxyphenyl-1-naphthylcarbinol (*J.*, 1946, 803), is converted into the neutral ester with particular ease; from its solution, *e.g.*, in chloroform, phthalic acid is deposited slowly in the cold, rapidly on warming. It does not yield a clear solution in aqueous alkali, the neutral ester being immediately deposited, nor can it be exactly titrated in alcoholic solution on account of partial hydrolysis. The neutral ester, however, is comparatively stable towards, or in, cold alkaline solutions. Though this is a general characteristic of esters, the comparison, in the present example, with the ready dismutation of the acid ester, suggests that the carbinyl cation is less easily separated from the neutral ester than from the acid ester. The suggestion is supported by the observation that the neutral ester is converted into the *p*-tolyl sulphone very much more slowly than is the acid ester, under comparable conditions.

In Part II (*J.*, 1942, 605) it is shown that the reaction which leads to the formation of the neutral di-*p*-methoxyphenylcarbinyl phthalate is not diverted by added anions (benzoate or octyl hydrogen phthalate), and these observations are also in agreement with the suggestion that the carbinyl radicals are more firmly held in the symmetrical di-ester than in other esters.

Since *tert.*-alcohols do not, as a rule, yield hydrogen phthalates by reaction with the acid anhydride in presence of pyridine, the reaction in presence of triethylamine has been investigated. No reaction occurred with linaloöl, ethylmethylphenylcarbinol, or triphenylcarbinol. Triphenylcarbinol may be unreactive in this sense on account of a very strong tendency to react by the opposite mechanism (separation of the hydroxyl ion), and so may ethylmethylphenylcarbinol, the hydrogen phthalate of which does not yield the corresponding neutral ester or sulphone because the carbinyl cations at once break down to αβ-dimethylstyrene. Alkyl–oxygen fission is less likely in linaloöl; the inertness of the *tert.*-alcohols may therefore be due in part to steric hindrance.

Experimental.

Di-p-*methoxyphenylcarbinyl Hydrogen Phthalate.*—A solution of the carbinol (Schackenberg and Scholl, *Ber.*, 1903, **36**, 655) (2·4 g.), phthalic anhydride (1·5 g., 1 mol.), and triethylamine (2 c.c., 1·5 mols.) in dry, peroxide-free dioxan (3 c.c.) was heated at 40° for 6 hours, then diluted with an equal volume of acetone, made slightly acid with hydrochloric acid, and further diluted with ice-water. The precipitate solidified (3·6 g.; m. p. 105—110°) and by crystallisation from benzene–light petroleum (1 : 1; 60 c.c.) was separated into the *hydrogen phthalate* (0·4 g.), m. p. 131—132° (Found: C, 70·5; H, 5·0. $C_{23}H_{20}O_6$ requires C, 70·4; H, 5·1%) and bisdi-*p*-methoxyphenylcarbinyl phthalate (2·0 g.), m. p. 110—115° (see below). In a similar experiment, but with one-third of the above quantities and without heating, the temperature of the mixture rose from 20° to 30° during 10 minutes. After a further 15 minutes, the mixture was treated as above, yielding a solid (1·1 g.), m. p. 118—120° which was raised to 128—129° by washing with benzene; *i.e.*, an improved yield of the hydrogen phthalate was obtained.

Solutions of the hydrogen phthalate in benzene or chloroform rapidly deposited phthalic acid, and the neutral ester was isolated from each solution. A cold solution of the hydrogen phthalate (0·161 g.) in acetone–ethyl alcohol–water required 7·59 c.c. of 0·1N-aqueous sodium hydroxide for titration to the phenolphthalein end-point (equivalent to titration of the carboxyl groups and 85% of the ester groups). Sodium hydroxide solution (5·0 c.c.; 0·1 N.) was then added, and the mixture heated at 90° for 2 hours, and the excess of alkali titrated; 1·10 c.c. had been consumed, equivalent to reaction with 17% of the ester groups. In other experiments, proportions of the ester groups ranging between 47 and 85% were titrated by the cold alkali.

Di-p-*methoxyphenylcarbinyl Phenylurethane.*—(i) A mixture of the carbinol (2·4 g.) and phenyl *iso*cyanate (1·2 g., 1 mol.) was gently warmed, then sealed for 10 days, the original emulsion then having solidified. The solid (3·5 g.) was recrystallised thrice from carbon tetrachloride–light petroleum, yielding the *urethane*, m. p. 111—112°. (Found: C, 72·3; H, 5·9; N, 3·7. $C_{23}H_{21}O_4N$ requires C, 72·7; H, 5·8; N, 3·9%). (ii) The carbinol (1·2 g.) was added slowly to a mixture of phenyl *iso*cyanate (0·6 g., 1 mol.) and dry triethylamine (0·7 c.c.). The clear solution became warm and after 5 minutes set solid (0·8 g.; m. p. 90—96°). Recrystallised as above, the urethane had m. p. 109—111°, alone or mixed with the first specimen.

Bisdi-p-*methoxyphenylcarbinyl Phthalate.*—The material of m. p. 110—115°, after recrystallisation from light petroleum (b. p. 60—80°), yielded the neutral *phthalate*, m. p. 114—115° (Found: C, 73·7; H, 5·6%; equiv., by hydrolysis with hot alcoholic potassium hydroxide, 621. $C_{38}H_{34}O_6$ requires C, 73·8; H, 5·5%; equiv., 618). A cold solution of the neutral ester in aqueous alcohol, made just alkaline to phenolphthalein with sodium hydroxide, retained its colour for several hours, indicating absence of hydrolysis. The neutral ester (0·4 g.) in ethyl ether (20 c.c.) was shaken with aqueous sodium hydroxide (10 c.c. of 0·3N.) for 1½ hours. The ethereal layer was separated, dried (Na_2SO_4), and concentrated, yielding the unchanged neutral ester (0·3 g.), m. p. and mixed m. p. 112—113°.

Di-p-*methoxyphenylcarbinyl* p-*Tolyl Sulphone.*—(i) *From the carbinyl hydrogen phthalate.* The hydrogen phthalate (0·39 g.) was added to a solution of sodium toluene-*p*-sulphinate (0·32 g.) in acetone (4 c.c.) and water (1·5 c.c.) at 20°. After 1 minute the clear solution was poured into water. The oil

which separated was extracted with ether, and the extract dried and concentrated, yielding the *sulphone* (0·35 g., 92%), m. p. 95—100°, raised by recrystallisation from ether–light petroleum to 109—110° (Found: S, 8·3. $C_{22}H_{22}O_4S$ requires S, 8·4%).

(ii) *From the neutral dicarbinyl phthalate.* A solution of the neutral ester (0·31 g.) in acetone (4 c.c.) was added to a solution of sodium toluene-*p*-sulphinate (0·32 g.) in water (1·5 c.c.). The mixture, after 10 minutes at 20°, was poured into water and treated as above, yielding unchanged neutral ester (0·22 g., 71%), m. p. and mixed m. p. 113—114°, and the *p*-tolyl sulphone (0·04 g., 5%), m. p. 96—98°; after recrystallisation, m. p. and mixed m. p. 105—106°.

Ethylmethylphenylcarbinyl Hydrogen Phthalate.—Powdered potassium (2·6 g.) was dissolved in a solution of the alcohol (11 g., 1·1 mol.) in benzene (20 c.c.). A warm solution of phthalic anhydride (10 g., 1 mol.) in benzene (60 c.c.) was added. After 30 minutes at 80° and 18 hours at room temperature, the mixture was poured into water. The separated benzene layer was washed with aqueous sodium hydrogen carbonate, and the combined aqueous layers were acidified with hydrochloric acid. The precipitated oil solidified (12 g., 60%), m. p. 105—110°; recrystallised from ether–light petroleum it yielded the *hydrogen phthalate*, m. p. 113—115° (Found: equiv., 300. $C_{17}H_{16}O_4$ requires equiv., 298), decomposing to phthalic acid and an unsaturated substance of b. p. 184—186° (Tiffeneau, *Ann. Chim.*, 1907, **10**, 362, records b. p. 186—187° for αβ-dimethylstyrene).

The solid (0·2 g.) which separated during 3 days from a solution of the hydrogen phthalate (0·5 g.) and N-sodium hydroxide (1·7 c.c.; 1 mol.) in water (10 c.c.) was unchanged hydrogen phthalate, m. p. and mixed m. p. 113—115°. Unchanged hydrogen phthalate (0·45 g.; m. p. and mixed m. p. 113—115°) also separated during 3 days from a mixture of the hydrogen phthalate (1·0 g.) in N-sodium hydroxide (3·3 c.c.; 1 mol.) and sodium toluene-*p*-sulphinate (0·85 g., 1·5 mols.) in water (17 c.c.).

A solution of the hydrogen phthalate (2 g.) in N-sodium hydroxide (6·7 c.c.; 1 mol.) was heated under reflux for 2 hours. The oil which separated was extracted with chloroform, and ozonised oxygen was passed through the dried extract. The ozonide was decomposed with water, and volatile products were swept by carbon dioxide into a solution of 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid. The dinitrophenylhydrazone of acetaldehyde (0·1 g.) was precipitated; m. p. and mixed m. p. after recrystallisation from ethyl alcohol, 165—167°. From the non-volatile fraction, the 2 : 4-dinitrophenylhydrazone of acetophenone (0·35 g.) was obtained, m. p. and mixed m. p. after recrystallisation from nitrobenzene, 235—240°.

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87. *The Oxidation of Phenols with Benzoyl Peroxide. Part II.*

By STANLEY L. COSGROVE and WILLIAM A. WATERS.

In contrast to *m*-4- and *m*-5-xylenols (*J.*, 1949, 3189), *m*-2-xylenol reacts with benzoyl peroxide in boiling chloroform, to give mainly 3 : 5 : 3′ : 5′-tetramethyldiphenoquinone (V). This involves the coupling of two phenolic radicals in the 4-position.

Mesitol yields 4-benzoyloxy-2 : 4 : 6-trimethyl*cyclo*hexa-2 : 5-dienone (VIII; R = Me, X = ·O·COPh) by the addition of a benzoate group in the 4-position to a phenolic radical, together with a trace of 3 : 5 : 3′ : 5′-tetramethylstilbenequinone (IX; R = Me), whilst a product of the latter type was the only substance that could be isolated after oxidation of 2 : 6-di-*tert.*-butyl-4-methylphenol.

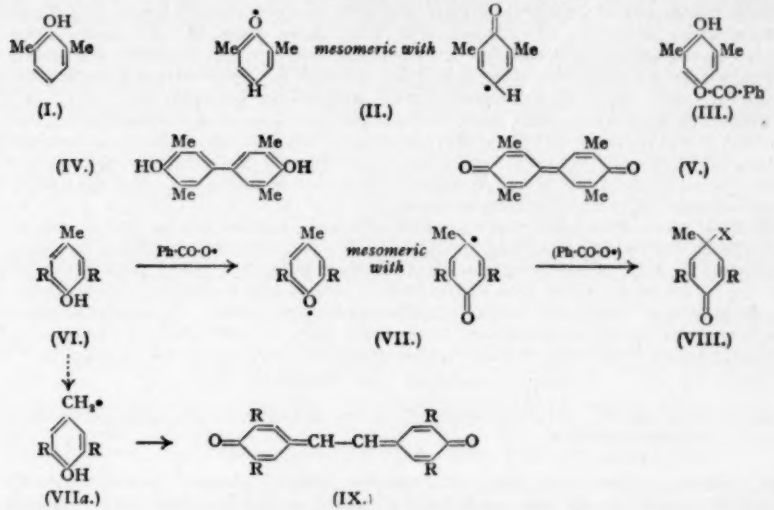
These oxidations are reviewed in connection with the rôles of phenols as inhibitors of autoxidation processes.

IN a previous paper (*J.*, 1949, 3189 *) we reported that on treatment with benzoyl peroxide in boiling chloroform solution phenol, the isomeric cresols, and *m*-4- and *m*-5-xylenol were oxidised to give the monobenzoates of pyrocatechol derivatives. We have now extended our study to *m*-2-xylenol (I), mesitol, and 2 : 6-di-*tert.*-butyl-4-methylphenol, in all of which both positions *ortho* to the hydroxy-group have been blocked by alkyl substituents.

Unlike the compounds previously studied, *m*-2-xylenol (I) gave 50% of the red 3 : 5 : 3′ : 5′-tetramethyl-4 : 4′-diphenoquinone (V), 10% of the corresponding 4 : 4′-dihydroxy-3 : 5 : 3′ : 5′-tetramethyldiphenyl (IV), and only 10% of the expected 5-benzoyloxy-*m*-2-xylenol (III). The formation of about 60% of the dimeric products (IV) and (V) substantiates our surmise of Part I

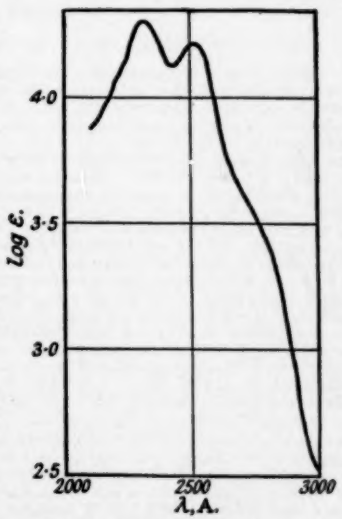
* Regarded as Part I of this series.

(*loc. cit.*) that oxidation by means of benzoyl peroxide proceeds by abstraction of a hydrogen atom by benzoate radicals and the transient formation of mesomeric phenol radicals such as (II).



Mesitol (VI; R = Me), after 12 hours' refluxing with benzoyl peroxide in chloroform, gave over 90% of 4-benzoyloxy-2 : 4 : 6-trimethyl*cyclo*hexa-2 : 5-dienone (VIII; R = Me, X = O·CO·Ph), with a trace of the red insoluble 3 : 5 : 3′ : 5′-tetramethylstilbenequinone (IX; R = Me) which had previously been prepared by Porter and Thurber (*J. Amer. Chem. Soc.*, 1921, **43**, 1194; cf. Goldschmidt and Bernard, *Ber.*, 1923, **56**, 1965) by oxidising mesitol with moist silver oxide. The production of (IX) may indicate that there can also be some slight side-chain attack at the *p*-methyl group to give the radical (VII*a*).

The "quinole" (VIII; R = Me, X = O·CO·Ph) has possibly been made by Bamberger and Rising (*Ber.*, 1900, **33**, 3633) by oxidation of mesitylhydroxylamine and benzoylation of the product, and perhaps by the oxidation of mesitol with Caro's acid (Bamberger, *Ber.*, 1903, **36**, 2028), but we have not been successful in repeating either of these preparations. In view of the great instability to water of the corresponding bromo-compound (VIII; R = Me, X = Br) (Fries and Brandes, *Annalen*, 1939, **542**, 48) the interpretation of Bamberger's work is open to doubt, and we have therefore substantiated the structural formula of our reaction product. Our material gives a red 2 : 4-dinitrophenylhydrazone, and its ultra-violet absorption spectrum (see figure), with absorption maxima at 2310 and 2510 A., has some similarities with that of an αβ-unsaturated ketone. Moreover, catalytic reduction converted our compound into mesitol and benzoic acid, whilst acid hydrolysis, followed by oxidation with ferric chloride and final sulphite reduction of the volatile quinone so formed, led to the isolation of both benzoic acid and 2 : 6-dimethylquinol, thus establishing the 4-position of the benzoate group (X in VIII). We failed to isolate any direct hydrolysis product corresponding to Bamberger's "mesityl-quinole" (VIII; R = Me, X = OH).



Maxima: 2310 *and* 2510 A.; ε = 20,400 *and* 16,600.

4-Methyl-2 : 6-di-*tert.*-butylphenol (VI; R = Bu^t) was attacked exceedingly slowly by benzoyl peroxide, and after 70 hours the only oxidation product isolated was 3 : 5 : 3′ : 5′-tetra-*tert.*-butylstilbene-4 : 4′-quinone (IX; R = Bu^t).

These results are of interest in connection with the use of alkylphenols as antioxidants (cf. Rosenwald, Hoatson, and Chenicek, *Ind. Eng. Chem.*, 1950, **42**, 162) since mesitol and 4-methyl-2 : 6-di-*tert.*-butylphenol are amongst the most potent antioxidants known. If chain-growth in an autoxidation process ceases because an active radical is destroyed by a reaction (*A*) which leads to a chemically inert aryl radical, •O–Aryl, of type (II) or (VII) (cf. Bolland, *Quart. Reviews*, 1949, **3**, 9; Bolland and Ten Have, *Trans. Faraday Soc.*, 1947, **43**, 201), then it would be expected that the first stage at least in the oxidation of mesitol or of 4-methyl-2 : 6-di-*tert.*-butylphenol would be easier than in less hindered phenols such as *p*-cresol, which is a relatively poor antioxidant. However, it now appears that the oxidation of *p*-cresol by benzoyl peroxide is the faster process.

We would therefore suggest that the reaction between *p*-cresol and benzoyl peroxide is not simply due to free benzoate radicals, though it must be started by a reaction of type (*A*). It may also include a chain-continuing reaction (*B*) between the *p*-tolyl radical and benzoyl peroxide molecules. This view accords with the findings of Nozaki and Bartlett (*J. Amer. Chem. Soc.*, 1946, **68**, 1686) and subsequent workers, who have shown conclusively that the decomposition of benzoyl peroxide in many solvents is, in no small part, a chain reaction and that typical " inhibiting agents " act, with varying degrees of efficacy, by reducing the chain length.

(*A*) $$\text{Rad}\bullet + \text{H–O–Aryl} \longrightarrow \text{Rad–H} + \bullet\text{O–Aryl}$$

(*B*) $$\underset{\left(\begin{smallmatrix}\text{tautomeric with}\\ \text{CH}_3\cdot\text{C}_6\text{H}_4\text{O}\bullet\end{smallmatrix}\right)}{\text{CH}_3\cdot\overset{\bullet}{\text{C}}_6\text{H}_3\cdot\text{OH}} + \text{Ph}\cdot\text{CO}\cdot\text{O}\cdot\text{O}\cdot\text{COPh} \longrightarrow \text{Ph}\cdot\text{CO}\cdot\text{O}\bullet + \text{CH}_3\cdot\text{C}_6\text{H}_3(\text{OH})\cdot\text{O}\cdot\text{COPh}$$

We therefore suggest, tentatively, that the less effective phenolic inhibitors (chiefly the monohydric phenols rather than derivatives of quinol or pyrocatechol) may yield aryloxy-radicals of an appreciable degree of chemical reactivity, and consequently that in autoxidation systems they may to some extent be able to act not only as chain-stopping agents but also as chain-transfer agents, by effecting dehydrogenations of the type of (*C*) :

(*C*) $$\text{Aryl–O}\bullet + \text{H–R} \longrightarrow \text{Aryl–O–H} + \bullet\text{R}$$

Experimental.

Oxidation of m-2-*Xylenol* (I).—The xylenol (12·2 g., 0·1 mol.) and benzoyl peroxide (24·2 g., 0·1 mol.) were refluxed in purified chloroform (300 ml.) for 4 hours. The solution was then washed with aqueous sodium hydrogen carbonate, the extracts were acidified, and benzoic acid (20·8 g., 0·17 mol.) was collected. Evaporation of the dried chloroform layer yielded a deep red gummy solid, which, when rubbed with ether (30 ml.), left 3 : 5 : 3′ : 5′-tetramethyl-4 : 4′-diphenoquinone (V) (6·1 g.) as a red insoluble powder. This crystallised from acetic acid in deep red needles, m. p. 210—215° (decomp.) (Found : C, 79·7; H, 6·3. Calc. for $C_{16}H_{16}O_2$: C, 80·0; H, 6·7%). Auwers and Markovits (*Ber.*, 1905, **38**, 226) have recorded the decomposition range as 207—217°. Evaporation of the ethereal solution gave a red gum (10·1 g.) which was distilled at 160—200° (oil-bath)/0·05 mm. The distillate, a mixture of *5-benzoyloxy*-m-2-*xylenol* (III) (1·5 g.) and 4 : 4′-dihydroxy-3 : 5 : 3′ : 5′-tetramethyldiphenyl (IV) (1·0 g.), was fractionally crystallised from light petroleum (b. p. 80—100°). The 5-benzoate crystallised in colourless plates, m. p. 140° (Found : C, 74·8; H, 5·9. $C_{15}H_{14}O_3$ requires C, 74·3; H, 5·8%). It was benzoylated in boiling pyridine solution and yielded 2 : 6-dimethylquinol dibenzoate, which crystallised from methanol in colourless needles, m. p. 116° unchanged on admixture with an authentic specimen prepared from 2 : 6-dimethylbenzoquinone by reduction and benzoylation. The 4 : 4′-dihydroxy-3 : 5 : 3′ : 5′-tetramethyldiphenyl proved to be identical with the substance obtained by reducing the diphenoquinone (V) with zinc dust in boiling acetic acid; it crystallised from methanol in colourless needles, m. p. 221° (Found : C, 79·1; H, 7·6. Calc. for $C_{16}H_{18}O_2$: C, 79·3; H, 7·45%) [diacetate, m. p. 172° (Found : C, 73·5; H, 6·8. Calc. for $C_{20}H_{22}O_4$: C, 73·6; H, 6·8%)]. Auwers and Markovits give the m. p.s as 220—221° and 174° respectively.

Oxidation of Mesitol.—Mesitol (13·6 g., 0·1 mol.) and benzoyl peroxide (24·2 g., 0·1 mol.) were refluxed in chloroform (250 ml.) for 12 hours. The bright red solution, worked up as above, gave benzoic acid (13·0 g., 0·11 mol.) and a 0·3 g. of deep-red, insoluble 3 : 5 : 3′ : 5′-tetramethylstilbene-4 : 4′-quinone (IX; R = Me). The latter was identical with the quinone obtained by oxidising mesitol in benzene solution with moist silver oxide (Porter and Thurber, *J. Amer. Chem. Soc.*, 1921, **43**, 1194) since samples prepared by both methods were readily reduced by zinc dust in boiling acetic acid to 4 : 4′-dihydroxy-3 : 5 : 3′ : 5′-tetramethylstilbene which crystallises from glacial acetic acid in colourless needles of m. p. and mixed m. p. 238°. Goldschmidt and Bernard (*Ber.*, 1923, **56**, 1963) give m. p. 225—235° and have verified the structure by synthesis. The dihydroxystilbene (1·2 g.) was hydrogenated at room temperature and atmospheric pressure in alcohol (50 ml.) over palladised charcoal (0·2 g.) to 4 : 4′-dihydroxy-3 : 5 : 3′ : 5′-tetramethyldibenzyl, colourless needles (from benzene), m. p. 168° (Found : C, 79·9; H, 8·1. Calc. for $C_{18}H_{22}O_2$: C, 80·0; H, 8·1%). Fries and Brandes (*Annalen*, 1939, **542**, 48) give m. p. 167°.

An ether-soluble neutral fraction from the oxidation of mesitol was a pale yellow oil (23·2 g.) which solidified on storage. It was purified by distillation at 0·02 mm. or, more simply, by treatment with half its weight of benzoyl chloride in boiling pyridine, and crystallised from methanol in colourless needles, m. p. 126—127° (Found: C, 74·8; H, 6·1. Calc. for $C_{14}H_{12}O_3$: C, 75·0; H, 6·2%). Its structure was established as 4-benzoyloxy-2 : 4 : 6-trimethyl*cyclo*hexa-2 : 5-dienone (VIII; R = Me, X = O·CO·Ph) thus: (i) it formed a red, very insoluble 2 : 4-dinitrophenylhydrazone, m. p. 270° (decomp.); (ii) on its thermal decomposition at 175°/30 mm., benzoic acid, m. p. and mixed m. p. 122, separated; (iii) on its oxidation (2·0 g.) with powdered potassium permanganate (3·7 g., *ca.* 4 O per mol.) in pure acetone (200 ml.) containing magnesium sulphate (6 g.), benzoic acid was again obtained; (iv) hydrogenation in alcohol at room temperature and pressure (palladised charcoal) gave benzoic acid, m. p. and mixed m. p. 122°, and mesitol, m. p. and mixed m. p. 71—72°, in equal amounts; (v) hydrolysis (of 2·0 g.) in a mixture of alcohol (30 ml.) and concentrated hydrochloric acid (20 ml.) for 3 hours under reflux gave a mixture from which ethyl benzoate (0·95 g.) was separated by steam distillation; the residue was treated with ferric chloride (2·0 g.) and again steam-distilled, and this distillate was treated with a little potassium iodide and then saturated with sulphur dioxide; after 24 hours the excess of sulphur dioxide was removed by boiling and the cooled solution was then extracted with ether; the extract yielded 2 : 6-dimethylquinol (0·15 g.), colourless needles (from xylene), m. p. 150° alone or mixed with an authentic specimen. Attempts, following Bamberger (*locc. cit.*), to synthesise the 4-benzoyloxy-2 : 4 : 6-trimethyl*cyclo*hexa-2 : 5-dienone (*a*) *via* its hydrolysis product (VIII; R = Me, X = OH) by the oxidation of mesitol with Caro's acid, or (*b*) by way of the reduction of nitromesitylene to mesitylhydroxylamine were unsuccessful.

Oxidation of 4-*Methyl*-2 : 6-*di*-tert.-*butylphenol.*—The phenol (11 g., 0·05 mol.) and benzoyl peroxide (12·1 g.) were refluxed in purified chloroform (150 ml.) for 70 hours. The bright red solution was then extracted with aqueous sodium hydrogen carbonate, the extracts were acidified, and benzoic acid (8·2 g., 0·67 mol.) was collected. Evaporation of the dried chloroform layer gave a bright red gum from which, by rubbing with ether (30 ml.), insoluble 3 : 5 : 3′ : 5′-*tetra*-tert.-*butylstilbene*-4 : 4′-*quinone* (IX; R = Bu^t) (1·0 g.) was removed by filtration. This crystallised from glacial acetic acid in crimson rods, m. p. 300° (decomp.) (Found: C, 82·7; H, 9·7. $C_{28}H_{40}O_2$ requires C, 82·9; H, 9·7%). Its reduction product, m. p. 230°, reoxidised rapidly on exposure to the air. The ethereal filtrate contained traces of unchanged reactants, but no other alkali-insoluble material could be isolated.

We thank Dr. D. G. Jones of Imperial Chemical Industries Limited (Billingham) for the gift of 4-methyl-2 : 6-di-*tert.*-butylphenol and for valuable information. We also thank Dr. F. B. Strauss for the microanalysis and for the determination of the ultra-violet absorption spectrum of 4-benzoyloxy-2 : 4 : 6-trimethyl*cyclo*hexa-2 : 5-dienone. One of us (S. L. C.) thanks the Department of Scientific and Industrial Research for a Maintenance Grant.

THE DYSON PERRINS LABORATORY, OXFORD. [*Received, September 9th*, 1950.]

88. *Diamidides. Part I. Derivatives of Triazapentadiene and Tetra-azaheptatriene.*

By F. C. COOPER, M. W. PARTRIDGE, and W. F. SHORT.

Numerous diamidides NR:CPh·NR′·CPh:NR″ and NRR′·CPh:N·CPh:NR″ have been prepared from the appropriate imidochloride and amidine (Ley and Müller, *Ber.*, 1907, **40**, 2950). *N*-Phenylbenzamidine and *N*-phenylbenzimidochloride afford decomposition products of the diamidide NH:CPh·NPh·CPh:NPh (VII) and, as minor product, the diamidide NHPh·CPh:N·CPh:NPh (VIII), the structure of which is proved by methylation to NPhMe·CPh:N·CPh:NPh, and by unambiguous synthesis. The triamidide NPh:CPh·N:CPh·NPh·CPh:NPh, a by-product in the preparation of the diamidide (VIII), is also obtained from *NN′*-diphenylbenzamidine and the imidochloride, NPh:CPh·N:CPhCl. The nascent imidosulphonate NPh:CPh·O·SO_2Ph, obtained by rearrangement of benzophenone oxime benzenesulphonate, and *N*-phenylbenzamidine afford the diamidide (VIII) (30%) and *NN′*-diphenylbenzamidine (38%), a decomposition product of the unstable diamidide (VII). The diamidide (VIII) is also obtained from *N*-phenylbenzamidine, benzanilide, benzenesulphonyl chloride, and pyridine, and the formation of by-products is explained by 1 : 4-addition of a phenylammonium ion to the system NRR′·CPh:N·CPh:NR″ or by interaction of the reciprocal pair. Diamidides NRR′·CPh:N·CPh:NR″ yield normal salts but di- and tri-amidides derived from NR:CPh·NR′·CPh:NR″ are readily decomposed by acids (HX) to NHR·CPh:NR′ and X·CPh:NR″. The bond structures of the diamidides are discussed in the light of their ultra-violet absorption spectra.

THE work of Barnes and Schoenheimer (*J. Biol. Chem.*, 1943, **151**, 123) and of Plentl and Schoenheimer (*ibid.*, 1944, **153**, 203) indicates that the primary source of nitrogen in the

pyrimidine and purine components of nucleic acids is ammonia, and that it is unlikely that their biosynthesis involves amidine-nitrogen. Nevertheless, the resemblance of the amidine group to the N–C–N system in pyrimidines and purines has provided a basis for a useful working hypothesis in the development of amidines having chemotherapeutic activity (Andrewes, King, and Walker, *Proc. Roy. Soc.*, 1946, **133**, *B*, 28). The extension of the amidine group to N–C–N–C–N appeared to us to be a subject of interest, since this system exhibits a closer formal resemblance to the carbon–nitrogen system in cytidine, cytosine, adenine, guanine, pteridines, *iso*alloxazines, and 4-aminoglyoxaline-5-carboxyamide, which has been suggested as an intermediate metabolite of purines by Shive, Ackermann, Gordon, Gretzendaner, and Eakin (*J. Amer. Chem. Soc.*, 1947, **69**, 725).

Few compounds possessing the open-chain N–C–N–C–N system have hitherto been described, apart from diguanide and biuret derivatives. Ley and Müller (*Ber.*, 1907, **40**, 2950) prepared "2 : 4 : 5-triphenylbiamidid" * (I) by interaction of *N*-phenylbenzimidochloride with benzamidine:

$$2CPh(:NH)\cdot NH_2 + Cl\cdot CPh{:}NPh \longrightarrow NH_2\cdot CPh{:}\overset{\oplus}{N}H_2\}\overset{\ominus}{Cl} + NPh{:}CPh\cdot N{:}CPh\cdot NH_2 \quad (I.)$$

These authors did not fulfil their promise of a further communication on the preparation of compounds of this type by the reaction of substituted imino-ethers with amidines. The direct addition of benzylamine to ethyl cyanotartronate was found by Curtiss and Nickell (*J. Amer. Chem. Soc.*, 1913, **35**, 887) to afford a very unstable compound, $C_{23}H_{21}O_{10}N_3$, to which they assigned the structure $C(OH)(CO_2Et)_2\cdot C(:NH)\cdot N(CH_2Ph)\cdot C(:NH)\cdot C(OH)(CO_2Et)_2$. Analogous compounds were not obtained from *iso*butylamine or ethylamine; diethylamine and dipropylamine afforded amidines, and aniline did not react. "Dibenzimidine" $NH{:}CPh\cdot NH\cdot CPh{:}NH$ (Pinner and Klein, *Ber.*, 1878, **11**, 4) and analogues obtained respectively from *p*-toluamidine (Glock, *Ber.*, 1888, **21**, 2650) and β-naphthamidine (Pinner, *Ber.*, 1892, **25**, 1434) and acetic anhydride were shown by Pinner (*Ber.*, 1892, **25**, 1624) to be triazines.

A number of new methods for the preparation of diamidides will be described in this series of memoirs, and we now record the preparation of aryltriazapentadienes by interaction of amidines with imidochlorides, ketoxime sulphonates, or imidosulphonates.

Apart from the example reported by Curtiss and Nickell (*loc. cit.*), there appears to be no record of the production of a diamidide by the addition of an amidine or an amidinium ion to a cyanide. The possible similarity of this reaction to some of the recently developed methods for the preparation of amidines led us to examine the reaction of phenylammonium benzenesulphonate with two equivalents of phenyl cyanide (cf. Oxley and Short, *J.*, 1946, 147) and of *N*-phenylbenzamidine and 4-methylsulphonylphenyl cyanide (cf. Oxley, Partridge, and Short, *J.*, 1948, 303). No evidence was found of the formation of a diamidide.

We have confirmed the production of 1 : 2 : 4-triphenyl-1 : 3 : 5-triazapenta-1 : 3-diene (I) in 72% yield by the method of Ley and Müller (*loc. cit.*), and have prepared 4-*m*-nitrophenyl-1 : 2-diphenyl-1 : 3 : 5-triazapenta-1 : 3-diene (II) from *m*-nitrobenzamidine (2 mols.) and *N*-phenylbenzimidochloride in ether. The fully substituted diamidides (III)—(VI) were obtained by prolonged (9—12 days) reaction of an *NN*- or *NN'*-disubstituted amidine (2 mols.) and the appropriate imidochloride in benzene, the yields being indicated in parentheses:

(II.) $NPh{:}CPh\cdot N{:}C(NH_2)\cdot C_6H_4\cdot NO_2(\text{-}m)$ (41%) (V.) $NMe{:}CPh\cdot NPh\cdot CPh{:}NPh$ (81%)

(III). $NMePh\cdot CPh{:}N\cdot CPh{:}NPh$ (82%) (VI.) $NPh{:}CPh\cdot NPh\cdot CPh{:}NPh$ (79%)

(IV.) $NPh_2\cdot CPh{:}N\cdot CPh{:}NPh$ (92%)

N-Methyl-*N*-phenylbenzamidine and *N*-phenylbenzimidochloride (1 mol.) in pyridine afforded only 17% of the diamidide (III), whereas *NN'*-diphenylbenzamidine and *N*-methylbenzimidochloride under these conditions gave 73% of the diamidide (V).

Methylation of *N*-phenylbenzamidine affords *N*-methyl-*N*-phenylbenzamidine and *N'*-methyl-*N*-phenylbenzamidine in the ratio 150 : 1 (Pyman, *J.*, 1923, **123**, 3359) and the

* The compound (I) was regarded by Ley and Müller as a derivative of the hypothetical substance "biformamidid" ($\overset{1}{NH}{:}\overset{2}{CH}\cdot\overset{3}{NH}\cdot\overset{4}{CH}{:}\overset{5}{NH}$) and was named "2 : 4 : 5-triphenylbiamidid." The name given to this compound in Beilstein's "Handbuch der organischen Chemie," 4th edn., XII, 266, is "*N*-phenyl-*N'*-(α-iminobenzyl)-benzamidin." The Editor has suggested the generic term "diamidide" for this class of compound and that individual examples should be named as derivatives of 1 : 3 : 5-triazapentadiene. Certain diamidides in which the position of the double bonds is ambiguous are arbitrarily named as derivatives of the 1 : 3-diene ($\overset{1}{NH}{:}\overset{2}{CH}\cdot\overset{3}{N}{:}\overset{4}{CH}\cdot\overset{5}{NH_2}$); on this sytem (I) becomes 1 : 2 : 4-triphenyl-1 : 3 : 5-triazapenta-1 : 3-diene. Compounds containing the chain N–C–N–C–N–C–N are similarly termed "triamidides" and are regarded as derivatives of 1 : 3 : 5 : 7-tetra-azaheptatriene.—W. F. S.

predominating *N*-methylation may be attributed to stabilisation of the anilo-form by the operation of the " Thiele factor " (Lapworth and Manske, *J.*, 1928, 2535).

$$\overset{\ominus}{I}\{\overset{\oplus}{N}H_2{\cdot}CPh{:}NPhMe \xleftarrow{MeI} NH_2{-}CPh{=}NPh \rightleftharpoons NH{=}CPh{-}NHPh \xrightarrow{MeI} NHMe{\cdot}CPh{:}\overset{\oplus}{N}HPh\}\overset{\ominus}{I}$$

(Major product) (Minor product)

Similarly, benzoylation affords *N*-benzoyl-*N*-phenylbenzamidine, although this is rearranged to *N'*-benzoyl-*N*-phenylbenzamidine on being heated (Wheeler, Johnson, and McFarland, *J. Amer. Chem. Soc.*, 1903, **25**, 787). In so far as an imidochloride may be regarded as an " alkylating agent " (cf. Oxley and Short, *J.*, 1948, 1514), it might therefore be expected that *N*-phenylbenzamidine and *N*-phenylbenzimidochloride would yield 1 : 2 : 3 : 4-tetraphenyl-1 : 3 : 5-triazapenta-1 : 4-diene (VII) as main product, 1 : 2 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 3-diene (VIII) being formed in smaller quantity :

$$\begin{array}{lll} NH_2{\cdot}CPh{:}NPh + NPh{:}CPhCl & \xrightarrow{-HCl} & NH{:}CPh{\cdot}NPh{\cdot}CPh{:}NPh \quad (VII.) \\ \downarrow\uparrow & & \\ NHPh{\cdot}CPh{:}NH + NPh{:}CPhCl & \xrightarrow{-HCl} & NPh{:}CPh{\cdot}NH{\cdot}CPh{:}NPh \\ & & \downarrow\uparrow \\ & & NHPh{\cdot}CPh{:}N{\cdot}CPh{:}NPh \quad (VIII.) \end{array}$$

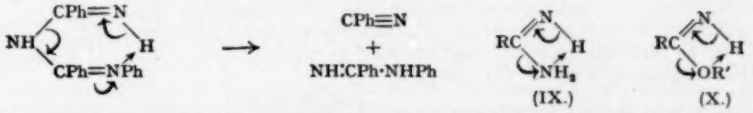
This expectation has been fulfilled to the extent that, whilst up to 16% of a diamidide has been isolated and shown to have the structure (VIII), the major products of the reaction were decomposition products of the diamidide (VII), which is therefore presumably formed in preponderating quantity but rapidly decomposed: $NH{:}CPh{\cdot}NPh{\cdot}CPh{:}NPh \longrightarrow PhCN + NPh{:}CPh{\cdot}NHPh$. This instability appears to be characteristic of many diamidides containing the group ·NR·CPh:NH (see below).

The products obtained from *N*-phenylbenzamidine (2 mols.) and *N*-phenylbenzimidochloride vary with the solvent; *e.g.*, in benzene solution 6% of the diamidide (VIII), 62% of *NN'*-diphenylbenzamidine, and 79% of *N*-phenylbenzamidine were obtained after 5 days; after 4 days 7% of a compound $C_{39}H_{30}N_4$, shown to be a triamidide (XV), was obtained in addition to 5% of the diamidide (VIII) and 38% of *NN'*-diphenylbenzamidine. The isolation of approximately equivalent quantities of *NN'*-diphenylbenzamidine (11%) and phenyl cyanide (13%) from the same reactants after 2 days in ether is consistent with the decomposition of the diamidide (VII), and those products could not be formed by a simple decomposition of the isomeric diamidide (VIII). *NN'*-Diphenylbenzamidine (19%) and the triamidide (16%) were obtained from *N*-phenylbenzamidine, *N*-phenylbenzimidochloride, and potassium carbonate in boiling acetone.

Evidence for the structure of the diamidide (VIII) was first sought by hydrolysis, but the compound was resistant to acids, 84% of unchanged diamidide and a little benzoic acid being recovered after 4 hours' boiling with concentrated hydrochloric acid. Boiling alcoholic potassium hydroxide hydrolysed the diamidide to *N*-phenylbenzamidine in agreement with the structure (VIII). The absence of the group ·NPh·CPh:NH in this diamidide is indicated by the recovery of 90% of the compound after an hour's heating at 190—200°, whereas under these conditions 1 : 2 : 4-triphenyl-1 : 3 : 5-triazapenta-1 : 3-diene (I) afforded *N*-phenylbenzamidine (83%). This decomposition is probably due to attraction of electrons by the anilo-nitrogen atom and, although the effect may be transmitted through the chain :

$$NH_2{\cdot}CPh{:}N{\cdot}CPh{:}NPh \rightleftharpoons H{-}N{=}CPh{-}NH{-}CPh{=}NPh \longrightarrow N{:}CPh + NH{:}CPh{\cdot}NHPh$$

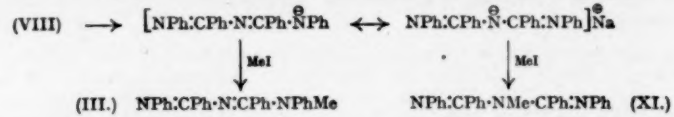
the process may be initiated by the formation of a hydrogen bond which determines the direction of the subsequent electronic displacements :



(IX.) (X.)

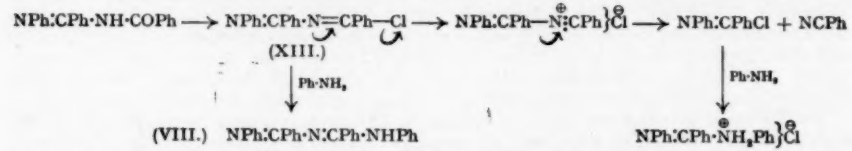
This interpretation brings the process into line with the production of cyanides by the decomposition of amidines (IX), imino-ethers (X; R' = Alk), and imidosulphonates (X; R' = SO_2Ar), represented for simplicity as taking place intramolecularly.

Conclusive evidence for the structure (VIII) was obtained by converting the diamidide by successive action of sodamide and methyl iodide into 5-methyl-1 : 2 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 3-diene (III), which was also synthesised by an unequivocal method:



The alternative methylation product (XI) was not detected, and the isomeric diamidide (V) was the sole product isolated (94%) when an attempt was made to obtain (XI) from *N'*-methyl-*N*-phenylbenzamidine and *N*-phenylbenzimidochloride. It is evident that the introduction of a *N'*-methyl group into *N*-phenylbenzamidine, by increasing the affinity of the *N'*-nitrogen atom for a proton, favours the anilo-form, so that the process, unlike the alkylation of *N*-phenylbenzamidine (above), becomes substantially unidirectional:

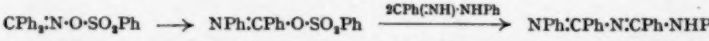
The preparation of 5-methyl-1 : 2 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 3-diene (III) (48%) from *N*-benzoyl-*N'*-phenylbenzamidine, phosphorus pentachloride, and methylaniline was undertaken as a model experiment for the unequivocal synthesis of the diamidide (VIII). 1-*p*-Chlorophenyl-2 : 4 : 5-triphenyl-1 : 3 : 5-triazapenta-1 : 3-diene (XII) (10%) was prepared similarly by using thionyl chloride and *p*-chloroaniline. Attempts to isolate the unstable intermediate *N*-(*N'*-phenylbenzimidyl)benzimidochloride (XIII) in analytically pure condition were unsuccessful, but the slightly impure material remaining after the removal of phosphoryl chloride afforded the diamidide (VIII) (30%) on reaction with aniline. *N*-Benzoyl-*N'*-phenylbenzamidine, phosphorus pentachloride, and aniline gave 12% of this diamidide in boiling benzene or 17% in cold chloroform, small quantities of *NN'*-diphenylbenzamidine and phenyl cyanide being also produced in each case. When the reaction was carried out in pyridine, the diamidide (5%), *NN'*-diphenylbenzamidine (77%), and phenyl cyanide (27%) were obtained, and the formation of these products can be accounted for by the following sequence of reactions:



The production of *NN'*-diphenylbenzamidine in this reaction cannot be explained by 1 : 2- or 1 : 4-addition of a phenylammonium ion to the diamidide (VIII), since fission of the resulting complex would also give *N*-phenylbenzamidine, a readily detected compound which was not present in the reaction product. *N*-Phenylbenzamidine is, however, produced in analogous transformations carried out at a higher temperature with the imidosulphonate corresponding to the imidochloride (XIII) and addition of a phenylammonium ion is therefore probably involved (see below).

N-Benzoyl-*NN'*-diphenylbenzamidine, phosphorus pentachloride, and ammonia afforded *NN'*-diphenylbenzamidine but no 1 : 2 : 3 : 4-tetraphenyl-1 : 3 : 5-triazapenta-1 : 4-diene (VII), confirming the conclusion that this diamidide is unstable. No 1 : 2 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 3-diene (VIII) was detected in the product, and this provides evidence against the assumption that when this diamidide is formed from *N*-phenylbenzamidine and *N*-phenylbenzimidochloride it is produced by rearrangement of the isomeric 1 : 4-diene (VII).

The method of preparing substituted amidines from ketoxime sulphonates and amines (Oxley and Short, *J.*, 1948, 1514) has now been extended to the production of 1 : 2 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 3-diene (VIII) (30%):



On account of the mesohydric tautomerism of *N*-phenylbenzamidine, the isomeric tetraphenyltriazapentadiene (VII) would be expected as a second product of this reaction; the *NN'*-di-

phenylbenzamidine (38%) obtained as a by-product was apparently formed by decomposition of this diamidide.

Since *N*-substituted imidosulphonates, formed by the action of sulphonyl chlorides on *N*-substituted amides, are sufficiently stable in the presence of pyridine to yield amidines on the subsequent addition of amines (Oxley, Peak, and Short, *J.*, 1948, 1618), it appeared likely that this series of reactions could be extended to the preparation of diamidides. In agreement with this, benzanilide, treated with benzenesulphonyl chloride in the presence of pyridine and then with *N*-phenylbenzamidine, afforded 1 : 2 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 3-diene (VIII) (17—23%) :

$$\mathrm{NHPh{\cdot}COPh} \longrightarrow \mathrm{NPh{:}CPh{\cdot}O{\cdot}SO_2Ph} + 2\mathrm{CPh(:NH){\cdot}NHPh} \longrightarrow \begin{cases} \mathrm{NPh{:}CPh{\cdot}N{:}CPh{\cdot}NHPh} & \text{(VIII.)} \\ \mathrm{NHPh{\cdot}CPh{:}\overset{\oplus}{N}H_2\}Ph{\cdot}\overset{\ominus}{SO_3}} & \end{cases}$$

The possibility of a further unambiguous synthesis of the diamidide (VIII) from the imidosulphonate of *N*-benzoyl-*N'*-phenylbenzamidine and aniline was examined. With 1 mol. of aniline, the products isolated from the reaction mixture were *N*-phenylbenzamidine (18%), *NN'*-diphenylbenzamidine (46%), benzanilide (8%), and 1 : 2 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 3-diene (VIII) (0·5%); with 2 moles of aniline, the reaction mixture afforded *N*-phenylbenzamidine (32%), *NN'*-diphenylbenzamidine (46%), benzanilide (7%), and phenyl cyanide (31%). We suggest that these reactions involve the formation of an imidosulphonate $\mathrm{NPh{:}CPh{\cdot}N{:}CPh{\cdot}O{\cdot}SO_2Ph}$ which behaves in exactly the same way as the imidochloride (XIII) in the scheme formulated above and yields benzanilide by hydrolysis during the working of the reaction mixture. The isolation of *N*-phenylbenzamidine in addition to *NN'*-diphenylbenzamidine suggests decomposition of the diamidide by addition of a phenylammonium ion :

$$\text{(VIII.)}\quad \mathrm{NPh{:}CPh{\cdot}N{:}CPh{\cdot}NHPh} + \mathrm{Ph{\cdot}\overset{\oplus}{N}H_3} \rightleftharpoons \mathrm{Ph{\cdot}NH_2} + \mathrm{NPh{:}CPh{\cdot}N{:}CPh{\cdot}\overset{\oplus}{N}H_2Ph}$$

$$\mathrm{NHPh{\cdot}CPh{:}N{\cdot}CPh(NHPh){\cdot}\overset{\oplus}{N}H_2Ph}$$

$$\mathrm{NPh{:}CPh{\cdot}\overset{\oplus}{N}H_3} \longleftarrow \mathrm{NPh{:}CPh{\cdot}\overset{\oplus}{N}H_2{\cdot}CPh(NHPh)_2} \longrightarrow \mathrm{NHPh{\cdot}CPh{:}NPh}$$

Evidence for the participation of the imidosulphonate was obtained by heating *N*-benzoyl-*N'*-phenylbenzamidine, benzenesulphonyl chloride, and pyridine and treating the resulting mixture with water. The products obtained were phenyl cyanide (28%), benzanilide (54%), benzenesulphonic acid (77%), and the diamidide (VIII) (1·6%). The mode of formation of (VIII) in this reaction is uncertain, but in view of its formation in this experiment, the synthesis of this diamidide from the imidosulphonate (XIV) can no longer be regarded as unambiguous.

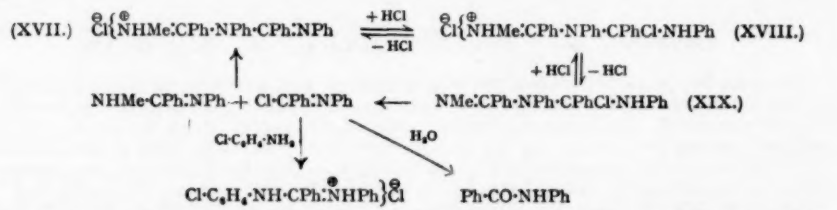
Evidence for the postulated fission of 1 : 2 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 3-diene (VIII) to give *N*-phenylbenzamidine and *NN'*-diphenylbenzamidine was sought by heating the diamidide with bases and their salts. The diamidide (84, 90, and 92% respectively) was recovered when heated for 90 minutes at 100° with aniline (2 mols.), aniline (2 mols.) and pyridine, or with pyridinium benzenesulphonate (1 mol.), but under the same conditions phenylammonium benzenesulphonate (2 mols.) in pyridine caused fission to *N*-phenylbenzamidine (92%) and *NN'*-diphenylbenzamidine (80%). This breakdown can be formulated as addition of a phenylammonium ion to $\rangle\mathrm{C{:}N{\cdot}}$ in the diamidide, but occurs more readily than analogous additions to the $\rangle\mathrm{C{:}N{\cdot}}$ group in amidines (Oxley and Short, *J.*, 1949, 449) or to the cyano-group in cyanides (Partridge and Short, *J.*, 1947, 390; Oxley, Partridge, and Short, *J.*, 1948, 303). Hickinbottom (*J.*, 1934, 1981) has shown that butadiene does not combine with aniline alone but reaction occurs in presence of phenylammonium chloride giving, *inter alia*, 1-anilinobut-2-ene by 1 : 4-addition of the elements of aniline. We therefore suggest that fission of the diamidide involves 1 : 4-addition of phenylammonium ion to the conjugated system of double bonds in the diamidide or of aniline to the diamidide ion as illustrated above. Similar additions of a phenylammonium ion to a conjugated system provide simpler explanations than those hitherto suggested for the decomposition of N^1-phenyldiguanide (Sugino, *J. Chem. Soc. Japan*, 1939, **60**, 411) and of dibenzoylamine, $(\mathrm{PhCO})_2\mathrm{NH}$ (Brunner, Seeger, and Dittrich, *Monatsh.*, 1924, **45**, 69), by phenylammonium chloride.

Ghadiali and Shah (*J. Univ. Bombay*, 1937, **6**, ii, 127) obtained a compound $C_{39}H_{30}N_4$ by the interaction of *N*-phenylbenzamidine and *N*-phenylbenzimidochloride in methanol–ether and, solely on the evidence of its nitrogen content and mode of formation, assigned to it the formula NPh:CPh·N:CPh·NPh·CPh:NPh (XV) in preference to the symmetrical structure $N(CPh{:}NPh)_3$ (XVI). The properties of this compound were in satisfactory agreement with those of the by-product which we obtained in the preparation of the diamidide (VIII), and an unambiguous synthesis showed that it is 1 : 2 : 4 : 5 : 6 : 7-hexaphenyl-1 : 3 : 5 : 7-tetra-azahepta-1 : 3 : 6-triene (XV) :

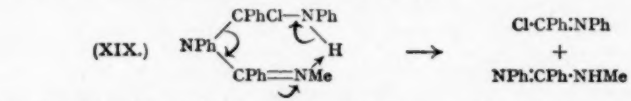
$$\text{(XIII)} + 2\text{NPh:CPh·NHPh} \longrightarrow \underset{\text{(XV.)}}{\text{NPh:CPh·N:CPh·NPh·CPh:NPh}} + \text{NHPh·CPh:}\overset{\oplus}{\text{N}}\text{HPh}\}\overset{\ominus}{\text{Cl}}$$

The triamidide (7%) produced in this way was accompanied by the diamidide (VIII) (9%), and repetition of Ghadiali and Shah's experiment afforded *N*-phenylbenzamidine (54%) and the triamidide (23%) and, in addition, the diamidide (VIII) (21%). The triamidide exhibited thermal stability and resistance to alkaline hydrolysis similar to that shown by the diamidide (VIII).

The diamidides (I), (III), and (VIII) afforded hydrochlorides and picrates but attempts to prepare the corresponding salts from the diamidide (V) and from the triamidide (XV) afforded decomposition products of these compounds. When the diamidide (V) was treated with hydrogen chloride in anhydrous benzene an oil separated, and the supernatant benzene solution afforded only *p*-chlorophenylammonium chloride and the unchanged diamidide (17%) on treatment with *p*-chloroaniline. Free hydrogen chloride and solvent were removed from the oil, and the residual gum when dissolved in benzene and treated successively with *p*-chloro-aniline and water afforded benzanilide (30%), *N*-methyl-*N'*-phenylbenzamidine (36%), *N*-*p*-chlorophenyl-*N'*-phenylbenzamidine (7%), and unchanged diamidide (17%). The following scheme accounts for the formation of these products if it is assumed that (*a*) the diamidide hydrochloride (XVII) is somewhat soluble in benzene and (*b*) the precipitated oil consists of the salt of the chloride (XVIII), which partially dissociates when excess of hydrogen chloride is removed, giving the chloride (XIX) (compare Hantzsch, *Ber.*, 1931, **64**, 667; Work, *J.*, 1942, 429), which then decomposes into *N*-methyl-*N'*-phenylbenzamidine and *N*-phenylbenzimido-chloride :



The following mechanism for the fission of the chloride (XIX) is analogous to that postulated for the thermal decomposition of the diamidide (I) :

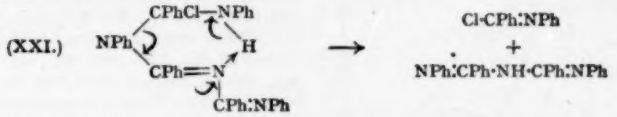


No *N*-*p*-chlorophenyl-*N'*-methylbenzamidine was detected in the product, and this appears to preclude the formation and decomposition of the alternative chloride, NHMe·CPhCl·NPh·CPh:NPh (XX).

A solution of 1-methyl-2 : 3 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 4-diene (V) in ethanolic lactic acid yielded, on the addition of aqueous sodium picrate, *NN'*-diphenylbenz-amidinium picrate (65%); the base and picric acid in benzene afforded *NN'*-diphenylbenz-amidinium picrate (44%) and *N*-methyl-*N'*-phenylbenzamidinium picrate (14%). The diamidide (V) and hydrochloric acid in aqueous ethanol afforded benzanilide (25%), *N*-methyl-*N'*-phenylbenzamidine (46%), and unchanged diamidide (25%). Benzanilide (91%) and *N*-methyl-*N'*-phenylbenzamidine (86%) were isolated from the mixture produced when the base (V) was treated successively with hydrogen chloride in chloroform and with water. It is

suggested that these decompositions occur by the mechanism illustrated above, although some of them could be interpreted by postulating direct hydrolysis of the diamidide. The isolation of both *NN'*-diphenylbenzamidinium picrate and *N*-methyl-*N'*-phenylbenzamidinium picrate indicates the formation of two addition compounds corresponding to the isomeric chlorides (XIX) and (XX).

The triamidide (XV) and ethanolic picric acid afforded the picrate of the diamidide (VIII) (59%), and the hydrochloride of this diamidide (67%) was precipitated by hydrogen chloride from a chloroform solution of the triamidide. The same hydrochloride (81%) was precipitated from a benzene solution of the triamidide, and *N*-*p*-chlorophenyl-*N'*-phenylbenzamidine (12%) was obtained when *p*-chloroaniline was added to the solution remaining after removal of the precipitated hydrochloride. The decomposition of the triamidide appears to be similar to that of the diamidide, but with the difference that the addition compound (XXI) is more readily decomposed than the corresponding chloride (XIX), so that *N*-phenylbenzimidochloride passes immediately into the benzene solution :



The isolation of the diamidide hydrochloride in these experiments with the triamidide is at variance with the results of Ghadiali and Shah (*loc. cit.*), who describe the preparation of the triamidide hydrochloride from the base and hydrogen chloride in benzene. Their hydro-

FIG. 1.

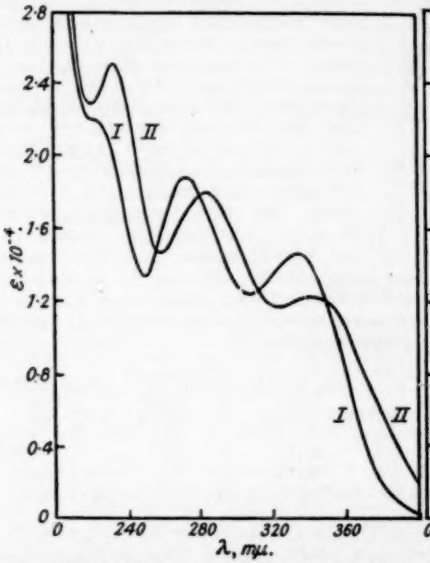


FIG. 2.

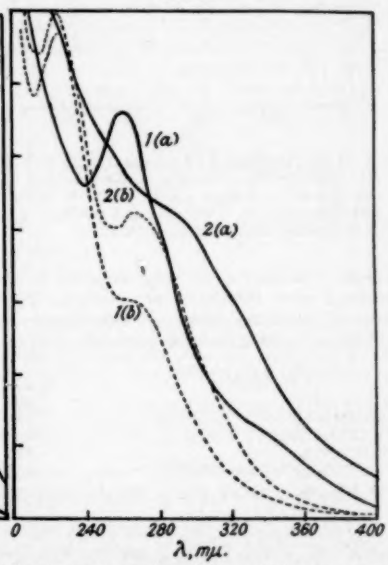


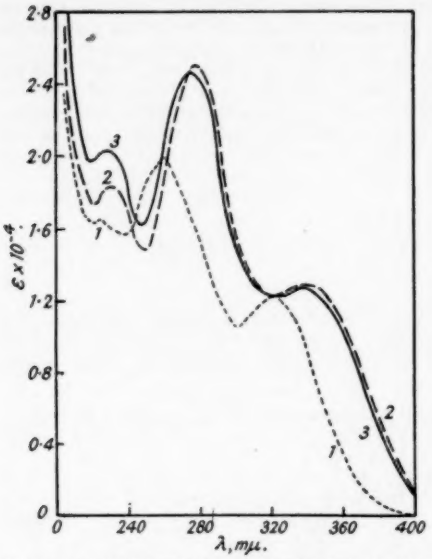
FIG. 1.—(*I*) 5-*Methyl*-1 : 2 : 4 : 5-*tetraphenyl*-1 : 3 : 5-*triazapenta*-1 : 3-*diene* (III). (*II*) 1 : 2 : 4 : 5 : 5-*Pentaphenyl*-1 : 3 : 5-*triazapenta*-1 : 3-*diene* (IV) *in* 0·1N-*ethanolic hydrochloric acid.*

FIG. 2.—(1) 1-*Methyl*-2 : 3 : 4 : 5-*tetraphenyl*-1 : 3 : 5-*triazapenta*-1 : 4-*diene* (V). (2) 1 : 2 : 3 : 4 : 5-*Pentaphenyl*-1 : 3 : 5-*triazapenta*-1 : 4-*diene* (VI); *a, with freshly prepared solution in* 0·1N-*ethanolic hydrochloric acid ; b, after* 5 *days' keeping.*

chloride melted at approximately the same temperature as the first m. p. of the diamidide hydrochloride, and the proportion of nitrogen found in their hydrochloride does not permit a clear distinction to be made between the diamidide and the triamidide hydrochlorides. The

ease with which the triamidide undergoes decomposition in the presence of hydrogen chloride accounts for the formation of the diamidide as a by-product in the previously described unambiguous synthesis of the triamidide from *N*-benzoyl-*N'*-phenylbenzamidine. Indeed, in other syntheses of this diamidide where the triamidide is formed simultaneously from the reaction between *N*-phenylbenzamidine and *N*-phenylbenzimidochloride, no evidence is available to exclude the possible formation of the diamidide *via* the triamidide.

FIG. 3.



(1) 1 : 2 : 4-*Triphenyl*-1 : 3 : 5-*triazapenta*-1 : 3-*diene* (I). (2) 1-p-*Chlorophenyl*-2 : 4 : 5-*triphenyl*-1 : 3 : 5-*triazapenta*-1 : 3-*diene* (XII). (3) 1 : 2 : 4 : 5-*Tetraphenyl*-1 : 3 : 5-*triazapenta*-1 : 3-*diene* (VIII) *in* 0·1N-*ethanolic hydrochloric acid.*

Evidence for the bond structure of the diamidides capable of exhibiting tautomerism was sought from their ultra-violet absorption spectra. In the spectra of the ions of the necessarily conjugated diamidides, 5-methyl-1 : 2 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 3-diene (III) and 1 : 2 : 4 : 5 : 5-pentaphenyl-1 : 3 : 5-triazapenta-1 : 3-diene (IV), three bands of decreasing intensity, at 220—235 mμ., 270—285 mμ., and 330—345 mμ., can be distinguished (Fig. 1). The last band is absent from the spectra of the ions of the isomeric unconjugated diamidides, 1-methyl-2 : 3 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 4-diene (V) and 1 : 2 : 3 : 4 : 5-pentaphenyl-1 : 3 : 5-triazapenta-1 : 4-diene (VI); a band at 262 mμ. is present in the unconjugated methyltetraphenyltriazapentadiene but the other bands are retained only as inflexions or bends [Fig. 2; curves 1(*a*), 2(*a*)]. The band at 330—345 mμ. is apparently characteristic of the conjugated diamidides. Absorption maxima at 220—230, 260—280, and 320—345 mμ. in the spectra of the ions of 1 : 2 : 4-triphenyl-1 : 3 : 5-triazapenta-1 : 3-diene (I), 1 : 2 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 3-diene (VIII), and 1-*p*-chlorophenyl-2 : 4 : 5-triphenyl-1 : 3 : 5-triazapenta-1 : 3-diene (XII) (see Fig. 3) indicate that the conjugated structures already arbitrarily assigned to these compounds in preference to the tautomeric non-conjugated structures are correct. Further evidence of conjugation is provided by the colour of the diamidides; all unconjugated bases are colourless, whereas all bases for which the ions show spectroscopic evidence of conjugation are yellow.

Compound.	$\lambda_{max.}$, mμ.	$\varepsilon_{max.} \times 10^{-4}$.	$\lambda_{max.}$, mμ.	$\varepsilon_{max.} \times 10^{-4}$.
NH:CPh·NHPh	234	1·81	*275* *	0·78
NMe:CPh·NHPh	—	—	*270*	0·88
NPh:CPh·NHPh	—	—	273	1·29
NH:CPh·NPh_2	225	1·73	270	0·629
NPh:CPh·N:CPh·NPh·CPh:NPh	235	3·33	272	2·66

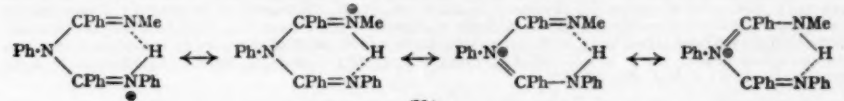
* Figures in italics refer to inflexions or bends. Solvent: 0·1N-ethanolic hydrochloric acid.

The significance of the bands in the regions of 230 and 270 mμ. is not clear. From the data summarised in the Table, it can be seen that these bands may also occur in the spectra of substituted amidines and in the triamidide. The band at 220—235 mμ. may possibly be assigned to the absorption of a C=N group, intensified and displaced, whereas benzenoid absorption may be responsible for the band in the region of 270 mμ. (cf. Barany, Braude, and Pianka, *J.*, 1949, 1898). In the spectrum of the triamidide there is some indication of a submerged maximum at 340—360 mμ. ($\varepsilon = 1{\cdot}3 \times 10^4$).

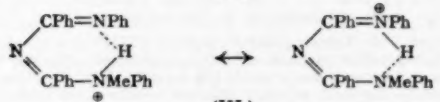
That the curves 1(*a*) and 2(*a*) given in Fig. 2 may refer to the spectra of the ions of these diamidides and not to decomposition products was demonstrated by observations on the change of these spectra with time. The results summarised in curves 1(*a*) and 2(*a*) were obtained

within 15 minutes of the preparation of the solution; a slight modification of both curves was apparent after 40 minutes. After 20 hours, the curve for 1 : 2 : 3 : 4 : 5-pentaphenyl-1 : 3 : 5-triazapenta-1 : 4-diene was identical with the curve 2(*b*) obtained when the spectroscopic solutions had been kept for 5 days. The change in 1-methyl-2 : 3 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 4-diene was slower.

A number of speculative suggestions may be made with regard to the remarkable differences in stability of certain diamidides. Conjugation appears to be a more important factor in stabilising these molecules or their ions than the formation of mesomeric cyclic hydrogen-bonded structures analogous to those put forward by Hunter and Roberts (*J.*, 1941, 820) for certain formazyl derivatives, since similar cyclic structures can be assigned to the unstable ion of 1-methyl-2 : 3 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 4-diene (V) and the stable ion of 5-methyl-1 : 2 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 3-diene (III) :

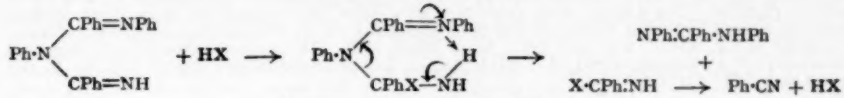


(V.)



(III.)

Our failure to obtain 1 : 2 : 3 : 4-tetraphenyl-1 : 3 : 5-triazapenta-1 : 4-diene (VII) may be ascribed to instability owing to the absence of conjugation, and its decomposition may be formulated in a manner analogous to the thermal decomposition of 1 : 2 : 4-triphenyl-1 : 3 : 5-triazapenta-1 : 3-diene (I). In the reactions in which its formation could have been expected, it may have undergone rapid decomposition *via* an unstable addition compound (XXII) similar to those (XIX and XXI) postulated in the decomposition of 1-methyl-2 : 3 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 4-diene and of the triamidide :



(XXII.) (X = Cl or ·O·SO_2Ph.)

Experimental.

Phenyl Cyanide and Phenylammonium Benzenesulphonate.—Phenylammonium benzenesulphonate and phenyl cyanide[3] (2 mols.) when heated together at 200—220° for 1 hour afforded *N*-phenylbenzamidine (91%). Since the mother-liquors from the isolation of the amidine were colourless when alkaline and afforded no yellow material on extraction with ethyl acetate, it was unlikely that a diamidide was a minor constituent of the product of the reaction.

N-Phenylbenzamidine and p-*Cyanophenyl Methyl Sulphone.*—When equimolecular quantities of these reagents were heated together at 180° for 4 hours, unchanged amidine (90%) and cyanide (93%) were recovered.

1 : 2 : 4-Triphenyl-1 : 3 : 5-triazapenta-1 : 3-diene (I) was obtained (72% yield) by interaction of *N*-phenylbenzimidochloride and benzamidine (2 mols.) in ether (Ley and Müller, *loc. cit.*) for 90 minutes; it had m. p. 146—147° (Ley and Müller record m. p. 152°) (Found : N, 14·0. Calc. for $C_{20}H_{17}N_3$: N, 14·0%). The hydrochloride had m. p. 245—247° (decomp.); Ley and Müller record m. p. 250° (decomp.) (Found : N, 12·3. Calc. for $C_{20}H_{17}N_3$,HCl : N, 12·5%). The *picrate* separated as needles from aqueous acetic acid, m. p. 167—168° with resolidification on further heating (Found : loss at 100°/vac., 1·75. Found, on dried material : N, 16·05. $C_{26}H_{20}O_7N_6$,$\frac{1}{2}H_2O$ requires H_2O, 1·7%. $C_{26}H_{20}O_7N_6$ requires N, 15·9%). The *benzenesulphonate* crystallised from aqueous ethanol in prisms, m. p. 207—207·5° (decomp.) (Found : N, 9·0. $C_{26}H_{23}O_3N_3S$ requires N, 9·2%).

This base (1 g.) when heated at 190—200° for 1 hour yielded a gum which smelt strongly of phenyl cyanide; *N*-phenylbenzamidine (0·55 g., 83%), m. p. and mixed m. p. 115—116°, was recovered from this material.

4-m-*Nitrophenyl*-1 : 2-*diphenyl*-1 : 3 : 5-*triazapenta*-1 : 3-*diene* (II).—To a solution of *N*-phenylbenzimidochloride (4·3 g.) in anhydrous ether (30 c.c.), a suspension of *m*-nitrobenzamidine (6·6 g., 2 mols.) in anhydrous ether (100 c.c.) was added. After 1 day's shaking, the solvent was evaporated and

m-nitrobenzamidinium chloride was extracted with hot water (20 c.c.). The residue, dissolved in hot ethanol (50 c.c.) and acidified with dilute hydrochloric acid, afforded **4-m-*nitrophenyl*-1 : 2-*diphenyl*-1 : 3 : 5-*triazapenta*-1 : 3-*diene hydrochloride*** (3·14 g., 41%), m. p. 216—218° (decomp.), raised by recrystallisation from ethanol to 219—221° (decomp.) (Found : N, 14·5. $C_{20}H_{16}O_2N_4$,HCl requires N, 14·7%). When the reactants were boiled in dry benzene for 1 hour, the yield was 47%.

5-Methyl*-1 : 2 : 4 : 5-*tetraphenyl*-1 : 3 : 5-*triazapenta*-1 : 3-*diene (III).—(i) A solution of *N*-phenylbenzimidochloride (4·3 g.) and *N*-methyl-*N*-phenylbenzamidine (8·4 g., 2 mols.) in dry benzene (90 c.c.) was kept for 11 days and filtered from the solid which slowly separated. The benzene was evaporated, and the residue, after crystallisation from aqueous ethanol, yielded ***5-methyl*-1 : 2 : 4 : 5-*tetraphenyl*-1 : 3 : 5-*triazapenta*-1 : 3-*diene*** (6·4 g., 82%) as yellow prisms, m. p. 104·5—105°, unchanged on recrystallisation from light petroleum [Found : N, 10·95%; *M* (Rast), 396. $C_{27}H_{23}N_3$ requires N, 10·8%; *M*, 389·5]. The benzene-insoluble solid consisted of *N*-methyl-*N*-phenylbenzamidinium chloride (3·9 g., 80%) which with alkali afforded the amidine, m. p. and mixed m. p. 85—86°. The ***hydrochloride*** of 5-methyl-1 : 2 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 3-diene separated very slowly as colourless prisms when hydrochloric acid was added to an aqueous ethanolic solution of the base, and had m. p. 234—234·5° (decomp.) (Found : N, 10·0. $C_{27}H_{23}N_3$,HCl requires N, 9·8%). The colloidal precipitate obtained on adding aqueous sodium picrate to a solution of the base in aqueous-ethanolic lactic acid crystallised when kept, and on recrystallisation from ethanol the pure ***picrate*** was obtained as orange-yellow prisms, m. p. 159·5—160·5° (Found : N, 13·45; $C_6H_3O_7N_3$, 36·95. $C_{27}H_{23}N_3,C_6H_3O_7N_3$ requires N, 13·6; $C_6H_3O_7N_3$, 37·05%).

Equimolecular quantities of *N*-phenylbenzimidochloride and *N*-methyl-*N*-phenylbenzamidine when brought into reaction in dry pyridine (15 mols.) afforded 5-methyl-1 : 2 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 3-diene (17%), m. p. and mixed m. p. 104·5—105°.

(ii) 1 : 2 : 4 : 5-Tetraphenyl-1 : 3 : 5-triazapenta-1 : 3-diene (VIII) (1·9 g.; see below), dissolved in dry benzene (40 c.c.), was boiled with a suspension of finely powdered sodamide (0·205 g., 1·05 mols.) in benzene (10 c.c.) until no more ammonia was evolved (2½ hours). Methyl iodide (1·4 g., 2 mols.) in dry benzene (10 c.c.) was added to the clear solution and the mixture was boiled for 90 minutes. The solvent was evaporated, and the residue, after extraction of sodium iodide with water, afforded on fractional crystallisation from ethanol 1 : 2 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 3-diene (0·75 g., 39%), m. p. and mixed m. p. 182—184°, and 5-methyl-1 : 2 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 3-diene (0·7 g., 36%), m. p. 104—105°, undepressed on admixture with the compound prepared by the foregoing procedure. Only unchanged 1 : 2 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 3-diene was recovered when attempts were made to carry out this methylation with methyl iodide in the presence of anhydrous potassium carbonate, or by heating the diene with a large excess of methyl iodide under pressure at 100° for 17 hours.

(iii) A solution of *N*-benzoyl-*N'*-phenylbenzamidine (7·5 g.) and phosphorus pentachloride (5·45 g., 1·05 mols.) in dry chloroform was kept at 20° for 5 hours, methylaniline (9·4 g., 3·5 mols.) was added, and, after being kept for 7 days, the solution was boiled for 90 minutes and evaporated to dryness under reduced pressure. The residue, after extraction with water, was crystallised from dilute aqueous ethanolic sodium hydroxide (charcoal) and gave 5-methyl-1 : 2 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 3-diene (4·2 g., 43%), m. p. and mixed m. p. 104·5—105°. The aqueous extract slowly deposited 5-methyl-1 : 2 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 3-diene hydrochloride (0·6 g., 5%), m. p. and mixed m. p. 233—234° (decomp.).

N-Benzoyl-N'-phenylbenzamidine.—The following procedure gave consistently better yields than the method of Wheeler, Johnson, and McFarland (*J. Amer. Chem. Soc.*, 1903, **25**, 787). Benzoyl chloride (11·7 g.) in dry, alcohol-free chloroform (50 c.c.) was added dropwise during one hour to a mechanically stirred solution of *N*-phenylbenzamidine (32·7 g., 2 mols.) in chloroform (170 c.c.). After being kept for 2 days, the suspension was filtered and evaporated; crystallisation of the residue from ethanol afforded *N*-benzoyl-*N'*-phenylbenzamidine (17—19·5 g., 68—78%), m. p. 143—144°. Wheeler *et al.* record m. p. 143° (Found : N, 9·35. Calc. for $C_{20}H_{16}ON_2$: N, 9·35%).

N-Methylbenzimidochloride was obtained from *N*-methylbenzamide and thionyl chloride in 39% yield, b. p. 65—67°/2·8 mm.; von Braun and Pinkernelle (*Ber.*, 1934, **67**, 1218) record b. p. 90—92°/13 mm. (Found : Cl, 22·95, 23·2. Calc. for C_8H_8NCl : Cl, 23·1%). Von Pechmann's method (*Ber.*, 1895, **28**, 2362) failed to give any of the desired product.

1-Methyl*-2 : 3 : 4 : 5-*tetraphenyl*-1 : 3 : 5-*triazapenta*-1 : 4-*diene (V).—*N*-Methylbenzimidochloride (3·1 g.) and *NN'*-diphenylbenzamidine (10·9 g., 2 mols.), dissolved in dry benzene (150 c.c.), were kept for 9 days and filtered. The yellow gum remaining after evaporation of the solvent afforded on crystallisation from ethanol **1-*methyl*-2 : 3 : 4 : 5-*tetraphenyl*-1 : 3 : 5-*triazapenta*-1 : 4-*diene*** (6·3 g., 81%), m. p. 147—148°; the pure compound was obtained as clusters of pale yellow needles, m. p. 148·5—149·5°, from light petroleum (b. p. 100—120°) [Found : C, 83·65; H, 5·75; N, 10·75; *M* (Rast), 384. $C_{27}H_{23}N_3$ requires C, 83·25; H, 5·95; N, 10·8%; *M*, 389·5]. On admixture with *NN'*-diphenylbenzamidine the m. p. was depressed to 123—125°. The benzene-insoluble material yielded *NN'*-diphenylbenzamidine (4·4 g., 41%), m. p. and mixed m. p. 146·5—147°, when dissolved in alcohol and treated with sodium hydroxide solution.

The yield was 73% when equimolecular quantities of *N*-methylbenzimidochloride and *NN'*-diphenylbenzamidine interacted in pyridine for 1 day. Unchanged *NN'*-diphenylbenzamidine (98%) was recovered when an attempt was made to carry out the reaction in acetone in the presence of anhydrous potassium carbonate.

A solution of *N*-phenylbenzimidochloride (4·3 g.) and *N*-methyl-*N'*-phenylbenzamidine (8·4 g., 2 mols.) in dry benzene (300 c.c.) was kept for 9 days and filtered. Solvent was evaporated from the filtrate, and

the residue, on crystallisation from ethanol, afforded 1-methyl-2 : 3 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 4-diene (7·35 g., 94%), m. p. and mixed m. p. 148—149°. The benzene-insoluble solid, when dissolved in water and added to excess of aqueous ammonia, afforded *N*-methyl-*N'*-phenylbenzamidine (3·2 g., 78%).

Double decomposition of an aqueous-ethanolic lactic acid solution of the triazapentadiene and aqueous sodium picrate yielded *NN'*-diphenylbenzamidinium picrate (65%), m. p. and mixed m. p. 217° (decomp.) (Found : N, 14·2; $C_6H_3O_7N_3$, 45·6. Calc. for $C_{19}H_{16}N_2,C_6H_3O_7N_3$: N, 13·95; $C_6H_3O_7N_3$, 45·7%). Equivalent quantities of the diamidide and picric acid in benzene afforded yellow needles, m. p. 200—208°, after sintering at 160°; fractional crystallisation of this material from benzene yielded *NN'*-diphenylbenzamidinium picrate (44%), m. p. and mixed m. p. 216·5—217° (decomp.), and *N*-methyl-*N'*-phenylbenzamidinium picrate (14%), m. p. 165—167°, undepressed on admixture with the authentic compound.

1 : 2 : 3 : 4 : 5-*Pentaphenyl*-1 : 3 : 5-*triazapenta*-1 : 4-*diene* (VI).—A solution of *N*-phenylbenzimidochloride (5·4 g.) and *NN'*-diphenylbenzamidine (13·6 g., 2 mols.) in dry benzene (200 c.c.) was kept for 13 days, filtered from precipitated *NN'*-diphenylbenzamidinium chloride (7·2 g.), and evaporated under reduced pressure; the residue, on crystallisation from ethanol, afforded 1 : 2 : 3 : 4 : 5-*pentaphenyl*-1 : 3 : 5-*triazapenta*-1 : 4-*diene* (8·9 g., 79%) as pale yellow needles, m. p. 146·5—148°, raised by further crystallisation from ethanol to 149—150°, depressed to 130—133° on admixture with *NN'*-diphenylbenzamidine (Found : N, 9·15. $C_{32}H_{28}N_2$ requires N, 9·3%).

NN-Diphenylbenzamidine was obtained in 34% yield by the aluminium chloride method (cf. Oxley, Partridge, and Short, *J.*, 1947, 1110) when the reactants were heated at 190—200° for 1 hour (cf. Oxley and Short, *J.*, 1949, 449).

1 : 2 : 4 : 5 : 5-*Pentaphenyl*-1 : 3 : 5-*triazapenta*-1 : 3-*diene* (IV).—The suspension obtained by interaction of *N*-phenylbenzimidochloride (2·7 g.) and *NN*-diphenylbenzamidine (6·8 g., 2 mols.) in benzene for 12 days was filtered and evaporated *in vacuo*. The residue, on being dissolved in ethanol and made alkaline with sodium hydroxide, slowly deposited dense clusters of yellow needles (5·2 g., 92%), m. p. 135—137°; recrystallisation from ethanol afforded 1 : 2 : 4 : 5 : 5-*pentaphenyl*-1 : 3 : 5-*triazapenta*-1 : 3-*diene*, m. p. 137·5—138° (Found : C, 85·3; H, 5·5; N, 9·3. $C_{32}H_{28}N_2$ requires C, 85·1; H, 5·5; N, 9·3%). The *picrate* crystallised as yellow prisms (from ethanol), m. p. 167—168° after sintering at 141° (Found : N, 12·1. $C_{32}H_{28}N_2,C_6H_3O_7N_3$ requires N, 12·4%).

1-*p*-*Chlorophenyl*-2 : 4 : 5-*triphenyl*-1 : 3 : 5-*triazapenta*-1 : 3-*diene* (XII).—A mixture of *N*-benzoyl-*N*-phenylbenzamidine (7·5 g.) and thionyl chloride (3·3 g., 1·1 mols.) was kept at 20° for 5 days and then heated at 100° for 2 hours; *p*-chloroaniline (6·4 g., 2 mols.), dissolved in dry benzene (30 c.c.), was added, and the mixture kept for 4 days. The solid (5·6 g.) which separated, after crystallisation from dilute ethanolic sodium hydroxide and repeated recrystallisation from benzene–light petroleum (b. p. 80—100°), yielded 1-*p*-*chlorophenyl*-2 : 4 : 5-*triphenyl*-1 : 3 : 5-*triazapenta*-1 : 3-*diene* (1 g., 10%), m. p. 177—179°, as pale yellow needles (Found : N, 10·05; Cl, 8·5. $C_{26}H_{20}N_3Cl$ requires N, 10·25; Cl, 8·7%).

1 : 2 : 4 : 5-*Tetraphenyl*-1 : 3 : 5-*triazapenta*-1 : 3-*diene* (VIII).—(i) *N*-Benzoyl-*N'*-phenylbenzamidine (7·5 g.) and phosphorus pentachloride (5·2 g., 1 mol.) reacted exothermally when mixed in dry, alcohol-free chloroform (40 c.c.). After 1 day, chloroform (25 c.c.) and ether (150 c.c.) were added, and the mixture rapidly extracted with water (3 × 50 c.c.) and dried ($MgSO_4$); on concentration under reduced pressure to about half its volume, the solution slowly yielded colourless prisms (2·1 g., 26%) which gradually decomposed above 160° (Found : labile Cl, 9·4. $C_{20}H_{15}N_2Cl$ requires Cl, 11·1%). A mixture of this *substance* (1 g.) with aniline (5 g., 17·5 mols.) dissolved in dry benzene (30 c.c.) was kept for 6 days; the precipitate which formed, after being dissolved in hot ethanol and treated with a slight excess of aqueous sodium hydroxide, afforded 1 : 2 : 4 : 5-*tetraphenyl*-1 : 3 : 5-*triazapenta*-1 : 3-*diene* (0·35 g., 30%) as pale yellow needles, m. p. 183·5—184° [Found : C, 83·1; H, 4·8; N, 11·3; *M* (Rast), 352. $C_{26}H_{21}N_3$ requires C, 83·15; H, 5·65; N, 11·2%; *M*, 375].

A solution of the base in ethanol, on the addition of aqueous hydrochloric acid, afforded the *hydrochloride*, colourless plates (from glacial acetic acid) which melted with effervescence at 250—254°, resolidified, and melted again at 300—306° (Found : N, 10·45. $C_{14}H_{22}N_3Cl$ requires N, 10·2%). The *picrate* crystallised as clusters of yellow needles from ethanol and had m. p. 190—191° (Found : N, 14·05. $C_{32}H_{24}O_7N_6$ requires N, 13·9%).

(ii) *N*-Benzoyl-*N'*-phenylbenzamidine (6·85 g.), phosphorus pentachloride (5 g., 1·05 mols.), and aniline (2·35 g., 1·1 mols.) were boiled together in dry benzene for 4 hours. The precipitate (1·2 g.) was crystallised from dilute ethanolic sodium hydroxide; these crystals afforded a dilute lactic-acid-soluble fraction from which *NN'*-diphenylbenzamidine (0·25 g., 4%) was isolated, and a dilute lactic-acid-insoluble fraction which after being crystallised from ethyl acetate–light petroleum (b. p. 80—100°) afforded 1 : 2 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 3-diene (0·25 g., 3%), m. p. and mixed m. p. 183—184°. The benzene mother-liquors after being evaporated *in vacuo* yielded a gum which smelt strongly of phenyl cyanide and from which a further quantity of the diamidide (0·8 g., 9%), m. p. and mixed m. p. 183—184°, was obtained by crystallisation from dilute ethanolic sodium hydroxide.

(iii) *N*-Benzoyl-*N'*-phenylbenzamidine (7·5 g.) and phosphorus pentachloride (5·45 g., 1·05 mols.), suspended in dry, alcohol-free chloroform (50 c.c.), gradually dissolved when kept at 20° for 1 hour; a solution of aniline (8·2 g., 3·5 mols.) in pure chloroform (50 c.c.) was added, and the mixture kept for 6 days. After removal of the phenylammonium chloride (5·85 g.) which crystallised, the solvent was evaporated under reduced pressure and the yellow gum which remained was crystallised from ethanol. Phenyl cyanide (1·4 g., 54%), b. p. 190—198°, was recovered from the mother-liquors by adding water and extracting with ether; it was characterised by conversion into *m*-nitrophenyl cyanide, m. p. and mixed m. p. 116—117°. The crystals (3·05 g.) from ethanol, when crystallised from dilute ethanolic sodium hydroxide and fractionally crystallised from ethanol, yielded 1 : 2 : 4 : 5-tetraphenyl-1 : 3 : 5-

triazapenta-1 : 3-diene (1·65 g., 17%), m. p. and mixed m. p. 182—183°, and *NN'*-diphenylbenzamidine (0·8 g., 12%).

(iv) A mixture of *N*-benzoyl-*N'*-phenylbenzamidine (7·5 g.), phosphorus pentachloride (5·45 g., 1·05 mols.), and anhydrous pyridine (5·95 g., 3 mols.) was heated at 100° for 135 minutes; aniline (4·65 g., 2 mols.) was added, and the heating continued for a further 90 minutes. The resulting semi-solid mass was extracted with hot water (150 c.c.), and the extract, which would have contained *N*-phenylbenzamidinium chloride had this been formed in the reaction, was made alkaline with aqueous ammonia; the precipitate (0·25 g.; m. p. 136—141°) afforded pure *NN'*-diphenylbenzamidine (0·15 g., 2%), m. p. and mixed m. p. 146—147°, on crystallisation from ethanol. Phenyl cyanide (1·5 g., 58%) was recovered from the ammoniacal mother-liquors by extraction with ether; no *N*-phenylbenzamidine was detected in this ethereal extract. The hot water-insoluble material when worked up in the usual way afforded *NN'*-diphenylbenzamidine (5·1 g., 75%) and 1 : 2 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 3-diene (0·5 g., 5%).

Attempted Synthesis of 1 : 2 : 3 : 4-*Tetraphenyl*-1 : 3 : 5-*triazapenta*-1 : 4-*diene* (VII).—A solution of *N*-benzoyl-*NN'*-diphenylbenzamidine (6·25 g.) and phosphorus pentachloride (3·8 g., 1·1 mols.) in dry benzene (150 c.c.) was boiled for 90 minutes. The solvent was evaporated at below 40° and the residue was shaken with saturated ethanolic ammonia (20 c.c.) for 20 hours. After removal of ammonium chloride, the filtrate was concentrated, and *NN'*-diphenylbenzamidine (2·8 g., 61%) crystallised.

Reaction of N-*Phenylbenzimidochloride with* N-*Phenylbenzamidine.*—(i) A solution of *N*-phenylbenzimidochloride (4·3 g.) and *N*-phenylbenzamidine (7·85 g., 2 mols.) in dry benzene (120 c.c.) was kept for 5 days. The solvent was evaporated, and the residue extracted with warm water (50 c.c.). Addition of aqueous ammonia to the aqueous extract afforded *N*-phenylbenzamidine (3·1 g., 79%), m. p. and mixed m. p. 112—113°. The water-insoluble material, which smelt strongly of phenyl cyanide, was dissolved in ethanol, made alkaline with aqueous sodium hydroxide, and poured into water. *NN'*-Diphenylbenzamidine was extracted from the precipitate by cold aqueous lactic acid and recovered as the base, m. p. and mixed m. p. 144—146° (3·35 g., 62%). Crystallisation from ethanol of the material insoluble in lactic acid afforded 1 : 2 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 3-diene (0·45 g., 6%), m. p. 183—184°, not depressed by authentic material (Found : N, 11·4. Calc. for $C_{28}H_{21}N_3$: N, 11·2%).

(ii) After 1 day the yield of 1 : 2 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 3-diene was 3%.

(iii) In a repetition of this experiment in which the period of reaction was 4 days, the basic material which was sparingly soluble in lactic acid was fractionally crystallised from ethanol and eventually separated into 1 : 2 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 3-diene (5%), m. p. 181—183° not depressed by the authentic compound, and 1 : 2 : 4 : 5 : 6 : 7-hexaphenyl-1 : 3 : 5 : 7-tetra-azahepta-1 : 3 : 6-triene (0·7 g., 7%), m. p. 178—179° not depressed on admixture with the authentic compound (see below).

(iv) *N*-Phenylbenzimidochloride (6·5 g.) and *N*-phenylbenzamidine (11·8 g., 2 mols.) were allowed to react in anhydrous ether for 2 days and the solvent was evaporated at room temperature. *N*-Phenylbenzamidinium chloride (56%) was extracted from the residue with warm water; the insoluble material on fractional crystallisation from ethanol afforded 1 : 2 : 4 : 5 : 6 : 7-hexaphenyl-1 : 3 : 5 : 7-tetra-azahepta-1 : 3 : 6-triene (2·8 g., 17%), m. p. and mixed m. p. 178·5—179·5°, and *NN'*-diphenylbenzamidine (0·9 g., 11%). Benzanilide (0·35 g., 6%) and phenyl cyanide (0·4 g., 13%), which was characterised by conversion into its *m*-nitro-derivative, were recovered from the mother-liquors.

(v) When the reaction was conducted in dry, alcohol-free chloroform, the products isolated were *N*-phenylbenzamidine (48%), *NN'*-diphenylbenzamidine (24%), 1 : 2 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 3-diene (16%), and 1 : 2 : 4 : 5 : 6 : 7-hexaphenyl-1 : 3 : 5 : 7-tetra-azahepta-1 : 3 : 6-triene (9%).

(vi) *N*-Phenylbenzimidochloride (4·3 g.) and *N*-phenylbenzamidine (3·9 g., 1 mol.), when boiled for 2 hours in dry acetone in the presence of anhydrous potassium carbonate, yielded 1 : 2 : 4 : 5 : 6 : 7-hexaphenyl-1 : 3 : 5 : 7-tetra-azahepta-1 : 3 : 6-triene (1·8 g., 16%) and *NN'*-diphenylbenzamidine (1·2 g., 19%).

Reaction of Benzophenone Oxime Benzenesulphonate with N-*Phenylbenzamidine.*—A solution of the benzenesulphonate (Oxley and Short, *J.*, 1948, 1514) (27 g.) and *N*-phenylbenzamidine (31·4 g., 2 mols.) in dry, alcohol-free chloroform (300 c.c.) was warmed gently till the exothermic reaction had subsided, and then boiled for 30 minutes. The solvent was evaporated under reduced pressure; a hot aqueous extract (2 × 100 c.c.) of the residue afforded *N*-phenylbenzamidine (11·5 g., 73%) when made alkaline with aqueous ammonia. The water-insoluble gum was crystallised from ethanolic hydrochloric acid. A hot ethanolic solution of the crystals was made alkaline with aqueous sodium hydroxide, and a mixture of colourless and yellow needles (17·1 g.) separated on cooling. *NN'*-Diphenylbenzamidine was extracted from this mixture by heating with lactic acid (10 c.c.) and water (100 c.c.), filtering, and adding aqueous ammonia; the yield was 8·1 g. (38%). Crude lactic-acid-insoluble 1 : 2 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 3-diene (9 g., 30%), m. p. 179—182°, afforded the pure compound (6·6 g., 22%), m. p. and mixed m. p. 183·5—184°, after crystallisation from ethanol. The diamidide prepared in this way was further characterised as its picrate, m. p. 190—191°, undepressed on admixture with the authentic compound.

Interaction of Benzanilide, Benzenesulphonyl Chloride, and N-*Phenylbenzamidine.*—A solution of benzanilide (4·9 g.) and benzenesulphonyl chloride (4·5 g., 1·03 mols.) in anhydrous pyridine (6 c.c., 3 mols.) was heated at 100° for 90 minutes; *N*-phenylbenzamidine (9·5 g., 1·95 mols.), dissolved in anhydrous pyridine (8 c.c.), was added, and the mixture heated for a further 3 hours. The residue left after evaporation of the pyridine under reduced pressure yielded, after crystallisation first from ethanol and then from dilute ethanolic sodium hydroxide, 1 : 2 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 3-diene

(VIII) (2·15 g., 23%), m. p. and mixed m. p. 183·5—184°. In another experiment, where the period of heating with *N*-phenylbenzamidine was 90 minutes, the yield was 17%.

Interaction of N-*Benzoyl*-N′-*phenylbenzamidine, Benzenesulphonyl Chloride, and Aniline.*—(i) A mixture of the benzamidine (7·5 g.), benzenesulphonyl chloride (4·4 g., 1 mol.), and anhydrous pyridine (6 g., 3 mols.) was heated at 100° for 2½ hours; aniline (4·65 g., 2 mols.) was added, and the mixture heated for a further 90 minutes. Next day the product was poured into water (250 c.c.) and concentrated hydrochloric acid (15 c.c.); the solid (4·3 g.) which separated gave *NN′*-diphenylbenzamidine (3·1 g., 46%), m. p. and mixed m. p. 146—147°, after being washed with ethanol and ether and crystallised from dilute ethanolic sodium hydroxide. The precipitate (0·55 g.) obtained on mixing the ethanol washings with the aqueous mother-liquors yielded benzanilide (0·35 g., 7%) after crystallisation from ethanol. From the remaining acid aqueous-alcoholic mother-liquors, phenyl cyanide (0·8 g., 31%), b. p. 189—193°, was isolated by extraction with ether and characterised as its *m*-nitro-derivative; *N*-phenylbenzamidine (1·6 g., 32%) was recovered by adding alkali.

(ii) The foregoing experiment was repeated with aniline (2·3 g., 1 mol.). The solid (5·2 g.) which separated when the reaction mixture was poured into water and hydrochloric acid afforded on crystallisation from dilute ethanolic sodium hydroxide and fractional crystallisation from ethanol *NN′*-diphenylbenzamidine (2·5 g., 37%) and 1 : 2 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 3-diene (VIII), m. p. and mixed m. p. 182—183° (0·05 g., 0·5%). Further fractional crystallisation from ethanol of the material in the first ethanol mother-liquors yielded benzanilide (0·4 g., 8%) and further *NN′*-diphenylbenzamidine (0·6 g., 9%). The aqueous hydrochloric acid mother-liquors gave crude *N*-phenylbenzamidine, m. p. 98—102° (1·15 g., 23%), on treatment with excess of aqueous ammonia; the pure compound (0·9 g., 18%) was obtained by crystallisation from light petroleum.

Interaction of N-*Benzoyl*-N′-*phenylbenzamidine and Benzenesulphonyl Chloride.*—A mixture of the benzamidine (7·5 g.), benzenesulphonyl chloride (4·4 g., 1 mol.), and anhydrous pyridine (6 g., 3 mols.) was heated at 100° for 2½ hours and poured into concentrated hydrochloric acid (15 c.c.) diluted with water (100 c.c.). Benzanilide (2·65 g., 54%) and phenyl cyanide (0·65 g., 28%) were recovered from an ethereal extract of the liquid. When dissolved ether was removed from the acid aqueous liquid, a solid (0·2 g.) separated; after crystallisation from dilute ethanolic sodium hydroxide this had m. p. 182·5—183·5°, undepressed on admixture with authentic 1 : 2 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 3-diene (VIII); the yield was 0·15 g. (1·6%). From the acid aqueous mother-liquor, benzenesulphonic acid was isolated as *S*-benzylthiuronium benzenesulphonate (77%), m. p. 147·5—148° (Chambers and Watt, *J. Org. Chem.*, 1941, **6**, 376, record m. p. 147·5—148·5°).

Decomposition of 1 : 2 : 4 : 5-*Tetraphenyl*-1 : 3 : 5-*triazapenta*-1 : 3-*diene* (VIII).—(i) After the pure base (1 g.) had been heated at 190—200° for 1 hour, its m. p. had fallen to 178—180°; crystallisation from alcohol afforded the pure compound (0·9 g.), m. p. and mixed m. p. 182·5—183·5°. (ii) A mixture of the base (1·9 g.), phenylammonium benzenesulphonate (2·5 g., 2 mols.), and anhydrous pyridine (1·6 g., 4 mols.) was heated at 100° for 90 minutes, poured into water (100 c.c.), and acidified with hydrochloric acid. From the precipitate, *NN′*-diphenylbenzamidine (1·1 g., 80%), m. p. 138—142°, was obtained by dissolution in dilute ethanolic sodium hydroxide and dilution with water; recrystallisation from ethanol yielded the pure compound (0·85 g., 62%), m. p. and mixed m. p. 146—147°. On the addition of aqueous ammonia the acid solution yielded *N*-phenylbenzamidine (0·9 g., 92%), m. p. and mixed m. p. 115—116°, after recrystallisation from benzene–light petroleum. (iii) The base (1·9 g.) did not dissolve completely when heated at 100° with aniline (0·95 g., 2 mols.) for 90 minutes; unchanged diamidide (1·6 g., 84%) was recovered from the reaction mixture. (iv) A mixture of the base (1·9 g.), aniline (0·95 g., 2 mols.), and pyridine (1·2 g., 3 mols.) formed a homogeneous solution when heated at 100° for 90 minutes; the precipitate obtained on addition of dilute hydrochloric acid afforded unchanged diamidide (1·7 g., 90%), m. p. and mixed m. p. 183—184°, on crystallisation from dilute ethanolic sodium hydroxide. (v) The diamidide (1·9 g.), pyridinium benzenesulphonate (1·2 g., 1 mol.), and pyridine (1·6 g., 4 mols.), after being heated together at 100° for 90 minutes, yielded unchanged diamidide (1·75 g., 92%). (vi) A solution of the diamidide (1·9 g.) in ethylene glycol (65 c.c.), water (3 c.c.), and potassium hydroxide (4 g.) was boiled (160—162°) for 3 hours; the yellow solution became almost colourless. After removal of the solvent, the residue yielded benzoic acid (0·9 g., 74%). (vii) After being boiled for 4 hours with concentrated hydrochloric acid, the diamidide was largely (84%) recovered unchanged; extraction of the hydrochloric acid with ether afforded benzoic acid (10%). (viii) When 1 : 2 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 3-diene (1·9 g.) was boiled with potassium hydroxide (4 g.) in water (4 c.c.) and ethanol (20 c.c.) for 25 hours, unchanged diamidide (1·45 g., 76%), m. p. 183—184°, crystallised on cooling. The solid (0·25 g.), m. p. 95—102°, which separated on pouring of the mother-liquors into water afforded *N*-phenylbenzamidine (0·15 g., 15%), m. p. and mixed m. p. 112—114°, after crystallisation from light petroleum.

1-*Methyl*-2 : 3 : 4 : 5-*tetraphenyl*-1 : 3 : 5-*triazapenta*-1 : 4-*diene* (V) *and Hydrogen Chloride.*—(i) On addition of hydrochloric acid to a solution of the diene in ethanol and dilution with water, benzanilide (25%) was obtained; the mother-liquors afforded *N*-methyl-*N*′-phenylbenzamidine (46%), m. p. and mixed m. p. 131—133°, and unchanged diamidide (25%) on addition of aqueous ammonia and fractional crystallisation of the precipitate from ethanol. (ii) From a solution of the base in chloroform which had been saturated with hydrogen chloride and kept for 2 days, benzanilide (91%) and *N*-methyl-*N*′-phenylbenzamidine (86%) were isolated. (iii) On saturation with dry hydrogen chloride of a solution of 1-methyl-2 : 3 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 4-diene (15 g.) in dry benzene (250 c.c.), a heavy, orange oil separated. The mixture was kept for 4 hours, and the benzene layer decanted and evaporated to dryness under reduced pressure. *p*-Chloroaniline (1·3 g.), dissolved in benzene (100 c.c.), was added to the residue, and the mixture kept for 4 days. *p*-Chlorophenylammonium chloride (1·6 g.) which crystallised was separated, and the solid (2·5 g., 17%), m. p. 140—144°, which was obtained by evaporating the filtrate afforded on crystallisation from ethanol unchanged diamidide (2·1 g., 14%), m. p. and mixed m. p. 148·5—149·5°.

Free hydrogen chloride was removed from the precipitated oil at 0·5 mm. over sodium hydroxide, and the resulting gum (15 g.) was dissolved in dry benzene (200 c.c.) containing *p*-chloroaniline (4·6 g.). The precipitate (11·25 g.) which formed during 5 days was separated into water-soluble and water-insoluble fractions; the former afforded *N*-methyl-*N'*-phenylbenzamidine (2·4 g., 30%), m. p. and mixed m. p. 131—133°, by precipitation with aqueous ammonia; and the latter, on fractional crystallisation first from dilute ethanolic sodium hydroxide and then from light petroleum (b. p. 80—100°), yielded benzanilide (0·4 g., 5%), m. p. and mixed m. p. 162—163°, and *N*-*p*-chlorophenyl-*N'*-phenylbenzamidine (0·8 g., 7%), m. p. 120—121°, undepressed on admixture with an authentic specimen. The benzene solution was evaporated, and the residue separated by means of dilute aqueous lactic acid into soluble and insoluble fractions. *N*-Methyl-*N'*-phenylbenzamidine (0·5 g., 6%) was recovered from the soluble fraction. By fractional crystallisation of the insoluble fraction from ethanol, benzanilide (1·9 g., 25%) and unchanged diamidide (2·6 g., 17%), m. p. and mixed m. p. 148—149°, were recovered.

N-p-*Chlorophenyl*-N'-*methylbenzamidine*.—*N*-Methylbenzamide (2·25 g.) was heated with thionyl chloride (2·4 g., 1·2 mols.) at 100° for 1 hour; excess of thionyl chloride was evaporated under reduced pressure at room temperature, and *p*-chloroaniline (4·25 g., 2 mols.), dissolved in dry benzene (50 c.c.), was added. The solid which separated during 4 days, after being basified with aqueous ammonia, yielded N-p-*chlorophenyl*-N'-*methylbenzamidine* (2·6 g., 63%), which crystallised as needles from light petroleum (b. p. 100—120°), and had m. p. 129—130° (Found: N, 11·25. $C_{14}H_{13}N_2Cl$ requires N, 11·45%). The *picrate*, needles from ethanol, had m. p. 179—180° (Found: N, 14·8. $C_{20}H_{16}O_7N_5Cl$ requires N, 14·8%).

1 : 2 : 4 : 5 : 6 : 7-*Hexaphenyl*-1 : 3 : 5 : 7-*tetra-azahepta*-1 : 3 : 6-*triene* (XV).—(i) A solution of *N*-benzoyl-*N'*-phenylbenzamidine (7·5 g.) and phosphorus pentachloride (5·45 g., 1·05 mols.) in dry, alcohol-free chloroform (50 c.c.) was shaken occasionally during 4 hours, and was then added dropwise at 0° to a solution of *NN'*-diphenylbenzamidine (23·8 g., 3·5 mols.) in pure chloroform (120 c.c.). *NN'*-Diphenylbenzamidinium chloride (18·9 g.) which had separated after 2 days was removed, and the yellow filtrate evaporated. The residue was stirred with dilute aqueous sodium hydroxide and then fractionally crystallised from ethanol to recover *NN'*-diphenylbenzamidine (4·65 g.) and a crop of yellow crystals (2·05 g.), m. p. 140—170°, which was separated into two fractions by means of hot aqueous lactic acid. The insoluble fraction (1·05 g.), m. p. 174—176°, afforded on crystallisation from ethanol 1 : 2 : 4 : 5 : 6 : 7-*hexaphenyl*-1 : 3 : 5 : 7-*tetra-azahepta*-1 : 3 : 6-*triene* (0·95 g., 7%) as yellow prisms, m. p. 178·5—179·5°, depressed to 160—165° on admixture with 1 : 2 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 3-diene [Found: C, 84·65; H, 5·85; N, 10·35%; *M* (Rast), 520. $C_{39}H_{29}N_3$ requires C, 84·45; H, 5·45; N, 10·1%; *M*, 554]. The lactic-acid-soluble fraction, after being basified with aqueous ammonia and crystallised from ethanol, gave 1 : 2 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 3-diene (0·8 g., 9%), m. p. and mixed m. p. 182—183°.

(ii) (cf. Ghadiali and Shah, *loc. cit.*) A solution of *N*-phenylbenzimidochloride (4·3 g.) in anhydrous ether was added slowly to a dry methanolic solution of *N*-phenylbenzamidine (7·85 g., 2 mols.), and the mixture kept for 5 days. The 1 : 2 : 4 : 5 : 6 : 7-hexaphenyl-1 : 3 : 5 : 7-tetra-azahepta-1 : 3 : 6-triene (2·6 g., 23%), m. p. and mixed m. p. 176—178°, which separated was collected. Evaporation of the filtrate and crystallisation of the water-insoluble fraction of the residue from ethanol afforded 1 : 2 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 3-diene (1·6 g., 21%), m. p. and mixed m. p. 182—183°. *N*-Phenylbenzamidine (4·25 g., 54%) was recovered from the water-soluble fraction.

1 : 2 : 4 : 5 : 6 : 7-Hexaphenyl-1 : 3 : 5 : 7-tetra-azahepta-1 : 3 : 6-triene (1 g.) was heated at 190—200° for 2 hours; the solid product was crystallised from ethanol and afforded the unchanged compound (0·85 g.), m. p. and mixed m. p. 178—179°. A solution of the triamidide (0·2 g.) in ethanol (15 c.c.), sodium hydroxide (0·1 g.), and water (0·5 c.c.) was boiled for 30 minutes and poured into water; the solid (0·19 g.) which was precipitated had m. p. 177—179°, undepressed on admixture with the triamidide. When equimolecular quantities of picric acid and the triamidide were mixed in ethanol and the solution was concentrated, 1 : 2 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 3-diene picrate (78%), m. p. 187—189°, crystallised; recrystallisation from ethanol afforded the pure picrate, m. p. and mixed m. p. 190—191°, in 59% yield. When a solution of the triamidide in ethanol was acidified with concentrated hydrochloric acid and poured into water, unchanged triamidide (63%), m. p. and mixed m. p. 176—178°, was precipitated.

An oil which slowly solidified was precipitated on saturating with hydrogen chloride a solution of the triamidide (0·75 g.) in benzene (30 c.c.). The benzene-insoluble solid, m. p. 245—250° (efferv.; second m. p. 295—300°), was crystallised from glacial acetic acid and gave 1 : 2 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 3-diene hydrochloride (0·45 g., 81%), m. p. 250—254° (efferv.; second m. p. 300—306°) (Found: N, 10·0. Calc. for $C_{39}H_{32}N_3Cl$: N, 10·2%). This hydrochloride was converted into the base, m. p. 182—183°, undepressed by authentic 1 : 2 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 3-diene. The benzene solution was evaporated to dryness under reduced pressure and the residue was dissolved in a solution of *p*-chloroaniline (0·35 g.) in benzene (25 c.c.). Next day, the solvent was evaporated; a solution of the resultant solid in water after being made alkaline with aqueous ammonia afforded *N*-*p*-chlorophenyl-*N'*-phenylbenzamidine (0·05 g., 12%), m. p. and mixed m. p. 121—122° after crystallisation from light petroleum.

Treatment of a solution of the triamidide in chloroform with hydrogen chloride afforded 1 : 2 : 4 : 5-tetraphenyl-1 : 3 : 5-triazapenta-1 : 3-diene hydrochloride in 67% yield.

We are indebted to Dr. W. F. Elvidge and Mr. L. Brealey for some of the spectroscopic data.

RESEARCH LABORATORIES, BOOTS PURE DRUG CO. LTD., NOTTINGHAM.
UNIVERSITY OF NOTTINGHAM. [*Received, September 13th*, 1950.]

89. *Chemical Actions of Ionising Radiations on Aqueous Solutions. Part VIII. Hydroxylation of Benzoic Acid by Free Radicals produced by X-Rays.*

By (Miss) H. Loebl, Gabriel Stein, and Joseph Weiss.

The hydroxylation of benzoic acid by free hydroxyl radicals produced by *X*-rays has been investigated. All three isomeric hydroxybenzoic acids were formed and their relative proportions have been estimated. The formation of salicylic acid has been investigated quantitatively, and its dependence on pH determined.

In previous papers it was shown that the action of ionising radiations, such as *X*-rays, on dilute aqueous solutions arises from the formation of free radicals (Weiss, *Nature*, 1944, **153**, 748; *Brit. J. Radiol.*, Suppl. 1, 1947; Stein and Weiss, *J.*, 1949, 3245). Reactions due to hydrogen atoms and hydroxyl radicals could be demonstrated and it was shown, in particular in the case of nitrobenzene (*J.*, 1949, 2074; 1950, 2704), that when oxygen-containing solutions of aromatic compounds are irradiated with comparatively small doses of *X*-rays the products are not only qualitatively, but also quantitatively, identical with those formed by the action of the hydrogen peroxide–ferrous salt (Fenton's) reagent, which is well known to produce free radicals. The use of penetrating radiations enables one to work quantitatively and within a pH range wider than is possible with Fenton's reagent. The present investigation is concerned with the action of free hydroxyl (and HO_2) radicals on dilute aqueous solutions of benzoic acid. In earlier, qualitative accounts (Stein and Weiss, *Nature*, 1948, **161**, 650; *J.*, 1949, 3245) we reported the isolation of *o*- and *p*-hydroxybenzoic acids from the products of the reaction in the approximate ratio of 1 : 2·5. The presence of the *m*-isomer could not be established then with certainty.

The action of γ-rays on aqueous solutions of benzoic acid has been investigated by Kailan (*Monatsh.*, 1920, **41**, 312) who isolated formic and oxalic acid, evidently the products of a far-reaching oxidation. The action of hydrogen peroxide on ammonium benzoate has been studied by Dakin and Herter (*J. Biol. Chem.*, 1907, **3**, 419) who have found the formation of approximately equal amounts of *o*-, *m*-, and *p*-hydroxybenzoic acid. Merz and Waters (*J.*, 1949, 2427), using Fenton's reagent, showed the formation of salicylic acid. Dakin considered the hydroxylation of aromatic compounds a typically biological reaction, which he attempted to reproduce *in vitro* by the use of hydrogen peroxide. However, of the metabolic products of benzoic acid, only the products of conjugation, *e.g.*, hippuric and benzoylglucuronic acids, were known until recently (cf. R. T. Williams, "Detoxication Mechanisms," Chapman and Hall, 1947), when Lederer (*J.*, 1949, 2115) identified *o*-, *m*-, and *p*-hydroxybenzoic acids in the urine of pregnant mares in the ratio 7 : 1 : 13. In the somewhat related case of the action of phenyl radicals on ethyl benzoate, Hey (*J.*, 1934, 1967) found that all three isomers are formed, the *p*-isomer predominating.

Our aim was to provide further quantitative experimental evidence on the problem of free-radical substitution in aromatic systems, and accordingly particular attention was paid to establishing which of the isomeric hydroxybenzoic acids was formed and their relative proportions. The mechanism of the reaction involved when ionising radiations act upon dilute aqueous solutions of aromatic compounds has been discussed in detail in previous papers (*loc. cit.*). The method of irradiation was the same as in the case of nitrobenzene (*loc. cit.*). Attempts to use the same analytical technique, *i.e.*, infra-red analysis, failed because in the present case chemical similarity made the quantitative separation of the relatively small amount of the products from the starting material impossible, whilst in the presence of a large excess of benzoic acid the bands of the products were masked in the infra-red spectrogram. Paper chromatography, according to Thorpe's method (Bray, Thorpe, and White, *Biochem. J.*, 1950, **46**, 271; personal communication from Dr. W. V. Thorpe) was therefore used for the separation and semi-quantitative estimation of the isomers. In this way it was shown that all three possible isomers were formed in the reaction, and in experiments carried out at pH $\sim$ 3, *i.e.*, in a solution of benzoic acid in water, the ratio of *o* : *m* : *p* was approximately 5 : 2 : 10.

By using colorimetric methods, the formation of the *o*-isomer, salicylic acid, has been investigated in greater detail. Fig. 1 shows that up to a dose of 5×10^4 E.U. the formation of

salicylic acid, in the presence of oxygen, is a linear function of the dose. Fig. 2 shows the dependence of the yield of salicylic acid on the pH; this curve is very similar to that obtained previously for the formation of phenol from benzene (*loc. cit.*). A solution of sodium benzoate has been used as the substrate in a method of dosimetry of ionising radiations (Day and Stein, *Nature*, 1949, **164**, 671), and Fig. 2 confirms that variations in pH around a mean value of pH ~8 will not affect the yield materially.

The results show that, as in the case of nitrobenzene, in the presence of the *meta*-directing carboxyl group hydroxylation takes place in all three possible positions, whilst in the case of the hydroxylation of phenol, carrying the powerfully *ortho-para*-directing hydroxyl group, the *m*-isomer is apparently not formed at all (to be published). In the present case the preponderance of the *p*- and the *o*- over the *m*-isomer is even more pronounced than for nitrobenzene, and the proportion of the *p*-isomer far exceeds that to be expected statistically. We hope to discuss the implications of our experimental results on completion of this series of papers on the free-radical hydroxylation of aromatic compounds.

Diphenyl was also produced, probably by a decarboxylation, which we have not investigated

FIG. 1.

Dependence of the yield of salicylic acid on the total dose (200 ml. of 0·2% benzoic acid solution; pH ~3).

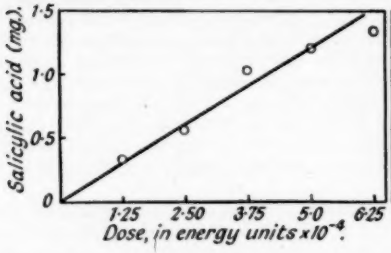
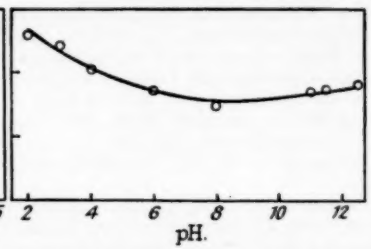


FIG. 2.

Dependence of the yield of salicylic acid on pH (200 ml. of 0·2% benzoic acid solution; constant dose of 5 × 10⁴ E.U.).



in detail. No attempt was made to identify any diphenyldicarboxylic acids that may have been formed in accordance with the reaction scheme which we have proposed previously (*loc. cit.*) for this type of reactions.

EXPERIMENTAL.

Irradiations.—These were carried out as described previously (Farmer, Stein, and Weiss, *J.*, 1949, 3241). A Victor Maximar *X*-ray set was used at 200 kv. and 15 ma., without filtration. The dose, determined according to Day and Stein's method (*loc. cit.*), was 2350 E.U./min., when 200 ml. of the solution were irradiated.

Benzoic Acid.—AnalaR material was used without further purification. Solutions were 0·2% with regard to benzoic acid, and the pH was adjusted by the addition of dilute sulphuric acid or sodium hydroxide as required. Unless otherwise stated, experiments were carried out with the solution of pure benzoic acid without further additions, at a pH ~3.

Isolation of diphenyl. Extraction of the neutralised solution yielded a neutral fraction, from which, after chromatography on alumina, crystals of diphenyl were obtained having m. p. 66° (uncorr.), not depressed on admixture with an authentic specimen.

Determination of salicylic acid. This was carried out in the irradiated solution directly, using Jorissen's reagent, or the ferric chloride method (cf. Snell, "Colorimetric Methods of Analysis," Vol. II) (see Figs. 1 and 2). The two methods gave identical results, when suitable allowances were made for blanks. A Spekker colorimeter was used for the analysis.

Separation and estimation of isomers. Purely chemical and infra-red analytical methods have proved unsuitable. To separate the *o*-isomer alone, the method of Bray, Thorpe, and White (*loc. cit.*) or that due to Evans, Parr, and Evans (*Nature*, 1949, **164**, 674) can be used. It is impossible in this manner to separate the *m*- from the *p*-isomer satisfactorily. For this purpose an improved method due to Thorpe (personal communication) was employed, using as solvent a mixture of butanol (4 vols.), pyridine (8 vols.), saturated aqueous sodium chloride (5 vols.), and aqueous ammonia (*d* 0·880, 3 vols.). The paper chromatogram was run upwards with this mixture on Whatman filter paper No. 1. On development with diazotised *p*-nitroaniline and sodium carbonate solutions, excellent separation of the three isomers was obtained and no other distinct spots were observable on the chromatogram, so that apparently, in agreement with our expectation, dihydroxybenzoic acids were not formed under the experimental conditions chosen. In order to obtain sufficient products for the chromatogram, six solutions (each containing 200 ml. of 0·2% benzoic acid solution at pH 3) were irradiated with a dose of

5×10^4 E.U., and the solutions were united and evaporated, after neutralisation, at a low temperature, in a vacuum, to the smallest possible volume at which precipitation did not take place. This volume was measured accurately, and an aliquot part run as described, in parallel with synthetic mixtures containing various amounts and relative proportions of the isomers. By a process of bracketing, the ratio of *o* : *m* : *p* approximately 5 : 2 : 10 was obtained, from a series of 5×6 irradiations. The yield of salicylic acid in one irradiation of 5×10^4 E.U. was 1·2 mg., that of the *p*- 2·5 mg., and of the *m*-isomer 0·5 mg., approximately. Other experiments were carried out in which, instead of several short irradiations, one solution was given a dose of the order of $\sim 10^6$ E.U. Under these conditions the oxygen available in the solution is insufficient and the greater part of the experiment occurs virtually in its absence. The resulting solution was treated as described above, and yielded a ratio of *o* : *m* : *p* approximately 6 : 4 : 10.

Our thanks are offered to Dr. W. V. Thorpe for advice regarding the paper chromatography, to Mr. G. Scholes for his assistance, to Dr. F. T. Farmer and Mr. M. J. Day of the Radium Department, R.V.I., for their help with the irradiations, and to the North of England Council of the B.E.C.C. for financial assistance.

KING'S COLLEGE, UNIVERSITY OF DURHAM,
NEWCASTLE-ON-TYNE.

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90. *Experiments relating to the Resolution of Tertiary Alcohols: the Resolution and Deamination of α-Naphthylphenyl-p-tolylmethylamine, and the Curtius, Hofmann, and Schmidt Reactions with 2-Methyl-2-phenylhexanoic Acid.**

By C. L. ARCUS, J. KENYON, and S. LEVIN.

α-Naphthylphenyl-*p*-tolylmethylamine has been resolved *via* the (+)- and (−)-camphorsulphonates. The (+)-amine hydrochloride with sodium nitrite yielded (±)-α-naphthylphenyl-*p*-tolylcarbinol. (±)-2-Methyl-2-phenylhexanoic acid * (I) gave, *via* the chloride and azide, (±)-2-amino-2-phenylhexane (II); the (+)-acid gave the (−)-amine. The amide of (I) with sodium hypochlorite gave (II) in low yield. Sodium azide in sulphuric acid–chloroform decomposed (I), yielding aniline (55%); the mechanism of this reaction is discussed. The preparation of some ω-alkylacetophenones is described.

NUMEROUS secondary alcohols have been resolved through the alkaloidal salts of their hydrogen phthalates (or succinates), but the many similar attempts with tertiary alcohols have failed, with the exception of *iso*butylethylmethylcarbinol (Doering and Zeiss, *J. Amer. Chem. Soc.*, 1948, **70**, 3966; 1950, **72**, 147). It was considered desirable to ascertain if amines of the type CRR′R″·NH_2, where R, R′, R″ are alkyl or aryl groups, could be obtained in optically active forms. No report of the resolution of such an amine or of its preparation by the degradation of an optically active acid CRR′R″·CO_2H has been found, although the following optically active amines have been prepared by the Hofmann reaction with amides the α-carbon atoms of which are tertiary and form part of an alicyclic ring: (+)-aminodihydrocampholytic acid (Noyes and Phillips, *Amer. Chem. J.*, 1900, **24**, 290), (+)-fenchelylamine hydrochloride (Wallach, *Annalen*, 1909, **369**, 81), (+)-aminolauronic acid (Weir, *J.*, 1911, **99**, 1270), (−)-amino*iso*dihydrocampholytic acid (Noyes and Nickell, *J. Amer. Chem. Soc.*, 1914, **36**, 118). Amines of similar type which were presumably optically active but for which no rotation data are given have been prepared as follows: camphelylamine, by the Hofmann reaction with the corresponding amide (Errera, *Gazzetta*, 1892, **22** (i), 205); and, by the Schmidt reaction with the corresponding acid, camphelylamine, fenchelylamine, dimethylcamphelylamine (von Braun, *Annalen*, 1931, **490**, 125; von Braun and Kurtz, *Ber.*, 1934, **67**, 225).

α-Naphthylphenyl-*p*-tolylmethylamine, prepared by the action of ammonia on the corresponding methyl chloride, has now been resolved by fractional crystallisation of the (+)- and the (−)-camphorsulphonate, the enantiomeric amines having $[\alpha]_{5893}^{17} \pm 1{\cdot}3°$ in carbon disulphide. Reaction of the (+)-amine hydrochloride (optical purity, 51%) with sodium nitrite gave optically inactive α-naphthylphenyl-*p*-tolylcarbinol. It is inferred that the intermediate

* Geneva numbering, CO_2H = 1.

carbonium cation is of sufficiently long life to yield equal amounts of (+)- and (−)-carbinol by reaction with a hydroxyl ion or water and that shielding by the released nitrogen molecule is here unimportant.

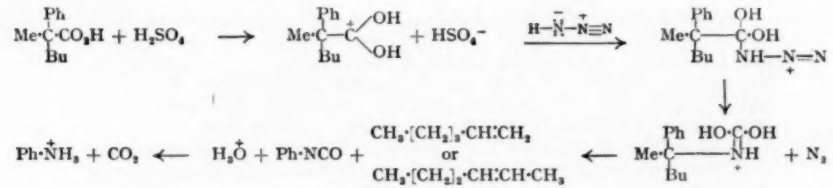
$$R{\cdot}NH_2{,}HCl + NaNO_2 \longrightarrow NaCl + H_2O + R{\cdot}N_2^+ + OH^-$$
$$R{\cdot}N_2^+ \longrightarrow R^+ + N_2;\ R^+ + OH^-\ (\text{or } H_2O) \longrightarrow ROH(+H^+)$$

Since Hofmann, Curtius, and Schmidt reactions with (+)-α-phenylpropionic acid gave (−)-1-phenylethylamine with a high degree of retention of asymmetry and of configuration (Arcus and Kenyon, *J.*, 1939, 916; Kenyon and Young, *J.*, 1941, 263; Campbell and Kenyon, *J.*, 1946, 25) it was decided to carry out these reactions with optically active 2-methyl-2-phenylhexanoic acid • (I). The chloride of the (±)-acid with sodium azide in aqueous acetone and in toluene gave (±)-2-amino-2-phenylhexane (II) in 27 and 25% yield respectively. Repetition of the reaction in aqueous acetone with the chloride of the (+)-acid (optical purity, 29%) gave (II) having α^{16}_{5893} −0·66° (homogeneous; *l.*, 0·5) which yielded a benzoyl derivative having $[\alpha]^{18}_{5893}$ +3·5° (in benzene).

From the reaction of the (±)-amide of (I) with sodium hypochlorite, the (±)-amine (II) was isolated as the benzoyl derivative in 10% yield; the reaction was not repeated with optically active material.

$CH_3{\cdot}[CH_2]_3{\cdot}CPhMe{\cdot}CO_2H$ (I.) $\qquad$ $CH_3{\cdot}[CH_2]_3{\cdot}CPhMe{\cdot}NH_2$ (II.)

Aniline (55% yield) was the sole basic product isolated from the reaction of the (±)-acid (I) with sodium azide in chloroform–sulphuric acid. Addition of bromine to the neutral products of reaction, and distillation, yielded a fraction the boiling point and bromine content of which indicated it to be dibromohexane(s). The most probable course of reaction appears to be the following:



It is intended to investigate in greater detail the mechanism of this reaction; it may be noted that (*a*) 1-methyl-1-phenyl-*n*-amyl *iso*cyanate is not abnormally unstable in the absence of sulphuric acid, because the Curtius reaction yielded the expected amine (II); (*b*) the Schmidt reaction with triethylacetic acid gave a mixture of lower amines, lower ketones, and triethylacetamide (Schuerch and Huntress, *J. Amer. Chem. Soc.*, 1949, **71**, 2238); (*c*) in contrast to the disintegration occurring with these two acids, trimethylacetic acid, 1-methyl*cyclo*hexanecarboxylic acid (Schuerch and Huntress, *ibid.*, p. 2233), the terpene acids investigated by von Braun (*loc. cit.*), and podocarpic acid (Briggs, De Ath, and Ellis, *J.*, 1942, 62) yield as the principal product of the Schmidt reaction the expected amine having the amino-group attached to a tertiary carbon atom.

The preparation of (±)-α-benzylpropiophenone, (±)-2-benzyl-2-methylhexanoylbenzene • and (±)-2-ethyl-2-methylhexanoylbenzene is described.

Experimental.

α-Naphthylphenyl-p-tolylmethylamine.—α-Naphthylphenyl-*p*-tolylcarbinol and its chloride were prepared by a modification of the method of Schlenk and Meyer (*Ber.*, 1919, **52**, 17), who record m. p. 109—110° and 142—144° for the carbinol and chloride respectively.

To a solution of α-naphthylmagnesium bromide, prepared from α-bromonaphthalene (45·5 g.) and magnesium (5·4 g.), in ether (135 ml.), heated under reflux, was added gradually, with stirring, a solution of phenyl *p*-tolyl ketone (43·5 g.) in ether (200 ml.). After 4 hours the mixture was cooled and decomposed with ice–ammonium chloride, yielding (±)-α-naphthylphenyl-*p*-tolylcarbinol, m. p. 109°. This material was dissolved in ether and a current of hydrogen chloride passed in for several hours. A little acetyl chloride was added to remove the water formed during the reaction. The solvent was distilled and the residue on crystallisation from light petroleum (b. p. 40—60°) yielded α-naphthylphenyl-*p*-tolylmethyl chloride, m. p. 142° (25 g., 33% yield from the ketone).

• Geneva numbering, $CO_2H = 1$.

Dry ammonia was passed through a solution of the chloride (25 g.) in benzene (550 ml.), until no more ammonium chloride separated. After filtration, and evaporation of the solvent, addition of light petroleum (b. p. 40—60°) to the residue gave a light brown powder, which on recrystallisation from alcohol gave (±)-α-*naphthylphenyl*-p-*tolylmethylamine*, small white needles, m. p. 127—128° (Found: C, 89·1; H, 6·5; N, 4·2. $C_{24}H_{21}N$ requires C, 89·1; H, 6·6; N, 4·3%).

Resolution. To a solution of (±)-α-naphthylphenyl-*p*-tolylmethylamine (21·0 g.) in alcohol (300 ml.) was gradually added a solution of (+)-camphorsulphonic acid (15·1 g.) in water (80 ml.); a salt (15·8 g.) gradually separated. Four recrystallisations from aqueous alcohol yielded a camphorsulphonate (8·2 g.), the amine from which had attained a constant rotation. This salt (4 g.) was agitated with 0·1N-sodium carbonate (300 ml.) and ether. The ethereal layer was repeatedly washed with aqueous sodium carbonate, then dried ($CaSO_4$), and the solvent evaporated. The residue was recrystallised from alcohol and gave α-naphthylphenyl-*p*-tolylmethylamine (2·2 g.), m. p. 128°, $[\alpha]_{5893}^{17}$ −1·3° (*c*, 3·7 in carbon disulphide). A similar resolution with (−)-camphorsulphonic acid yielded α-naphthylphenyl-*p*-tolylmethylamine having $[\alpha]_{5893}^{17}$ +1·3° (*c*, 4·7 in carbon disulphide).

On passing dry hydrogen chloride through a solution of (±)-α-naphthylphenyl-*p*-tolylmethylamine in dry ether, the hydrochloride separated as a white precipitate, m. p. 150—155° (decomp.). The amine was recovered nearly quantitatively on treating the hydrochloride with aqueous sodium carbonate. A specimen of the amine having $[\alpha]_{5893}^{17}$ +1·0° (*c*, 5·5 in carbon disulphide) yielded a hydrochloride having $[\alpha]_{5893}^{17}$ +1·5° (*c*, 6·7 in water), +1·3° (*c*, 6·1 in 0·1N-hydrochloric acid).

Deamination. To a solution of (±)-α-naphthylphenyl-*p*-tolylmethylamine hydrochloride (4·2 g.) in water (75 ml.) was added a solution of sodium nitrite (2·4 g.) in water (25 ml.). A white crystalline mass separated; water (50 ml.) was added and the whole boiled. Benzene was then added and the mixture stirred with heating under reflux for 24 hours. The benzene layer was washed repeatedly with 3N-hydrochloric acid and with warm water, dried ($CaSO_4$), and treated with charcoal and with alumina. After removal of the benzene under reduced pressure, the residue (2·9 g.) was allowed to crystallise slowly from ligroin, (±)-α-naphthylphenyl-*p*-tolylcarbinol (1·2 g., 31%), m. p. 109° alone or mixed with authentic material, being obtained (Found: C, 88·3; H, 6·2. Calc. for $C_{24}H_{20}O$: C, 88·7; H, 6·4%). Repetition with α-naphthylphenyl-*p*-tolylmethylamine hydrochloride having $[\alpha]_{5893}$ +1·0° (in water) gave optically inactive carbinol.

Curtius, Hofmann, and Schmidt Reactions with 2-Methyl-2-phenylhexanoic Acid.—To a solution of α-phenylpropionitrile (79 g.; b. p. 114°/16 mm.; prepared according to Campbell and Kenyon, *loc. cit.*) and *n*-butyl bromide (85 g.) in dry benzene (100 ml.) was added a suspension of sodamide (24·5 g.) in benzene. After an initial brisk reaction the whole was heated, with stirring, on a steam-bath for several hours. Water was then added and the benzene layer repeatedly washed with water and dried ($CaSO_4$). After distillation of the benzene, the residue was distilled and gave 1-*methyl*-1-*phenylamyl cyanide*, b. p. 147°/16 mm. (80 g., 71%) (Found: C, 83·2; H, 9·2; N, 7·6. $C_{13}H_{17}N$ requires C, 83·3; H, 9·2; N, 7·5%).

The nitrile (17 g.) was heated under reflux for 10 days in a solution of potassium hydroxide (16 g.) in alcohol (90 ml.) and water (25 ml.). The alcohol was then distilled off, water added, and the whole acidified and extracted with benzene. Evaporation of the benzene extract yielded a mixture of the acid, the amide, and some unchanged nitrile. Fractionation of the mixture gave the acid still containing some amide. This material was dissolved in excess of alkali and repeatedly extracted with chloroform; acidification of the alkaline solution gave 2-methyl-2-phenylhexanoic acid, b. p. 173°/16 mm. (Found: (equiv., 208·0. Calc. for $C_{12}H_{17}{\cdot}CO_2H$: equiv., 206·3).

Resolution of the acid was carried out according to Conant and Carlson (*J. Amer. Chem. Soc.*, 1932, **54**, 4055), by recrystallising the quinine salt from aqueous alcohol until the acid obtained on decomposing a portion of the salt had attained a constant rotation. The fully-active acid had the rotatory powers recorded in the table.

λ:			4358	4678	4800	5086	5461	5893	6438		
2-Methyl-2-phenylhexanoic acid.											
Solvent.	*c.*	Temp.									
None	—	15°	α (*l*, 0·5):							+8·65°	
Et_2O	6·41	15°	[α]:		+23·3°	+19·4°	+19·3°	+16·4°	+13·8°	+11·6°	+9·4°
CS_2	1·00	17°	[α]:						+26·0°	+21·4°	
2-Amino-2-phenylhexane.											
None	—	16°	α (*l*, 0·5):	−1·70°	−1·32°	−1·25°	−1·03°		−0·83°	−0·66°	−0·56°
Et_2O	1·00	17°	[α]:						−1·3°	−1·2°	
CS_2	1·00	17°	[α]:							−2·3°	
0·5N-HCl	1·00	16°	[α]:							+0·3°	

2-Methyl-2-phenylhexanoyl chloride (11·1 g.), b. p. 123°/18 mm. (Found: equiv., 114. Calc. for $C_{12}H_{17}{\cdot}COCl$: equiv., 112·3), was prepared by the action of thionyl chloride (50 ml.) on the acid (11·5 g.). To an ice-cooled solution of the acid chloride (15·4 g.) in acetone (150 ml.) was added, with stirring, a solution of sodium azide (5 g.) in water (20 ml.). After ½ hour sufficient water was added to give a homogeneous solution and stirring was continued for 1 hour. Water (200 ml.) was added and the oil which separated was extracted with ether and dried ($CaSO_4$); after filtration, toluene was added, the ether distilled off, and the remaining solution refluxed for several hours. Concentrated hydrochloric acid (150 ml.) was added and the whole heated with stirring on a steam-bath for 6 hours. After extrac-

tion with benzene, the aqueous layer was evaporated to small volume, and excess of sodium hydroxide solution was added. An oil separated which was extracted with ether; evaporation of the latter and distillation of the residue yielded 2-amino-2-phenylhexane (2·7 g.), b. p. 127°/18 mm., which by Schotten–Baumann benzoylation gave *2-benzamido-2-phenylhexane* (3·4 g.) which separated from benzene–ligroin in small silky needles, m. p. 146—147° (Found: C, 80·9; H, 8·5; N, 4·9. $C_{19}H_{23}ON$ requires C, 81·0; H, 8·2; N, 4·9%). Evaporation of the toluene layer (above) and addition of ether gave a material which separated from benzene–light petroleum (b. p. 40—60°) as small crystals (0·6 g.) of *2-amino-2-phenylhexane hydrochloride*, m. p. 144—147°, soluble in water (Found: Cl, 16·5. $C_{12}H_{20}NCl$ requires Cl, 16·1%). It yielded a benzoyl derivative having m. p. 146—147° alone or mixed with the above benzoyl derivative. By this procedure 2-methyl-2-phenylhexanoic acid (9·7 g.) having $[\alpha]_{5893}^{15}$ +6·3° (*c*, 1·00 in carbon disulphide) gave (−)-2-amino-2-phenylhexane (1·6 g.) having the rotatory powers recorded in the table, which yielded a benzoyl derivative having $[\alpha]_{5893}^{15}$ +3·5° (*c*, 1·00 in benzene).

To a solution of 2-methyl-2-phenylhexanoyl chloride (8·8 g.) in dry toluene (40 ml.) was added sodium azide which had been activated with hydrazine hydrate according to Nelles (*Ber.*, 1932, **65**, 1345). The mixture was heated under reflux with stirring for 8 hours, cooled, and filtered, the solvent removed by distillation, and the residue heated for several hours on the steam-bath with concentrated hydrochloric acid. The aqueous layer was made alkaline with sodium hydroxide solution and extracted with ether; after drying ($CaSO_4$) and removal of the ether, the residue gave on distillation 2-amino-2-phenylhexane, b. p. 127°/18 mm., which was converted into the benzoyl derivative (1·7 g.), m. p. 146—147°.

2-Methyl-2-phenylhexanoyl chloride (12 g.) was gradually added to aqueous ammonia (200 ml.; *d* 0·88), and the whole evaporated on a steam-bath. The oil so obtained was extracted with benzene and dried (NaOH), the solvent removed, and the *2-methyl-2-phenylhexanoamide* distilled; it had b. p. 187°/15 mm. (Found: C, 75·6; H, 8·8; N, 6·5. $C_{13}H_{19}ON$ requires C, 76·0; H, 9·3; N, 6·8%). The amide (2·0 g.) was shaken with sodium hypochlorite solution (60 ml.; prepared from 2·2 g. of chlorine and 6 g. of sodium hydroxide) at 40° until it dissolved. The solution was then heated to 80°; a yellow oil separated which was extracted with benzene, concentrated hydrochloric acid was added to the extract, the benzene was evaporated, and the residue heated for several hours. After extraction with ether, the aqueous solution was evaporated to small volume; Schotten–Baumann benzoylation then gave 2-benzamido-2-phenylhexane, m. p. 146—147° (0·3 g.).

To a solution of 2-methyl-2-phenylhexanoic acid (5·5 g.) in chloroform (45 ml.) was added concentrated sulphuric acid (13 ml.); sodium azide (2·1 g.) was added, with vigorous stirring, at such a rate that the temperature was kept at 40—45°. Stirring was continued for 1 hour with heating on the steam-bath, and the reaction mixture poured into water. The aqueous layer was repeatedly extracted with small quantities of chloroform and then made alkaline with aqueous sodium hydroxide. An oil was liberated which was extracted with benzene, the extract dried (K_2CO_3), and the benzene distilled off. The residue on distillation yielded aniline (1·2 g.), b. p. 80°/18 mm. (Found: C, 77·4; H, 7·7; N, 14·7. Calc. for C_6H_7N: C, 77·4; H, 7·5; N, 15·1%), identified by conversion into toluene-*p*-sulphonanilide, m. p. 103°, and acetanilide, m. p. 113°.

The chloroform extract was subjected to alkaline extraction [whereby unchanged acid (0·6 g.) was recovered] and dried (K_2CO_3), and bromine added gradually until a brown colour just persisted. The chloroform solution was washed with aqueous sodium thiosulphate and the solvent evaporated off; the residue on distillation gave dibromohexane, b. p. 95°/15 mm. (Found: Br, 64·3. Calc. for $C_6H_{12}Br_2$: Br, 65·4%). Repetitions of the Schmidt reaction with the reactants in the same proportions at temperatures between 37° and 54° gave aniline in similar yields.

To a solution of propiophenone (170 g.) in dry benzene (650 ml.) was slowly added a suspension of sodamide (51 g.) in benzene; the whole was heated under reflux with stirring for several hours until no further ammonia was evolved. Benzyl chloride (160 g.) was then added with continued stirring and heating. Water was added to the cooled reaction mixture, the benzene layer washed with water and dried (Na_2SO_4), and the solvent evaporated off. The residue on distillation yielded (±)-*α-benzylpropiophenone* (159 g.), b. p. 181°/10 mm. (Found: C, 85·7; H, 7·4. $C_{16}H_{16}O$ requires C, 85·7; H, 7·2%).

Reaction, under similar conditions, of (±)-α-benzylpropiophenone (155 g.) with sodamide (27 g.) and *n*-butyl bromide (95 g.) gave (±)-*2-benzyl-2-methylhexanoylbenzene* (58 g.), b. p. 192—196°/13 mm. (Found: C, 85·2; H, 8·1. $C_{20}H_{24}O$ requires C, 85·6; H, 8·6%).

Under similar conditions propiophenone (53 g.) in benzene (650 ml.), sodamide (53 g.), and *n*-butyl bromide (186 g.) in benzene (100 ml.) yielded (±)-2-methylhexanoylbenzene (148 g.), b. p. 123°/23 mm. This material (148 g.) in benzene (650 ml.) was treated similarly with sodamide (38 g.) and ethyl iodide (122 g.), the latter being run beneath the surface of the reaction mixture; there was obtained (±)-*2-ethyl-2-methylhexanoylbenzene* (100 g.), b. p. 140°/13 mm. (Found: C, 82·2; H, 10·0. $C_{15}H_{22}O$ requires C, 82·5; H, 10·2%).

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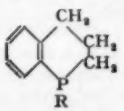
BATTERSEA POLYTECHNIC, LONDON, S.W.11. [*Received, October 23rd*, 1950.]

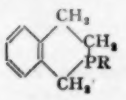
91. *The Preparation of* 1-*Substituted* 1 : 2 : 3 : 4-*Tetrahydrophosphinolines and* 2-*Substituted* 1 : 2 : 3 : 4-*Tetrahydroisophosphinolines.*

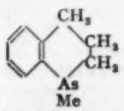
By M. H. Beeby and Frederick G. Mann.

The syntheses of 1-ethyl-1 : 2 : 3 : 4-tetrahydrophosphinoline and of 2-ethyl-1 : 2 : 3 : 4-tetrahydro*iso*phosphinoline are described by methods which can undoubtedly be applied to many other alkyl(or aryl)-substituted derivatives. The *iso*phosphinoline is both more basic and more readily oxidised than the phosphinoline isomeride.

It is noteworthy that although 1-substituted 1 : 2 : 3 : 4-tetrahydrophosphinolines (I) and 2-substituted 1 : 2 : 3 : 4-tetrahydro*iso*phosphinolines (II) have not hitherto been recorded, their arsenic analogues have been prepared and investigated in detail. Thus Burrows and Turner (*J.*, 1921, **119**, 430) have shown that methyl-3-phenylpropylchloroarsine, $Ph{\cdot}[CH_2]_3{\cdot}AsMeCl$, undergoes ready cyclisation by aluminium chloride to 1 : 2 : 3 : 4-tetrahydro-1-methylarsinoline (III). Holliman and Mann (*J.*, 1943, 547) and Beeby, Cookson, and Mann (*J.*, 1950, 1917) have shown that *o*-2-bromoethylbenzyl bromide, $Br{\cdot}CH_2{\cdot}C_6H_4{\cdot}CH_2{\cdot}CH_2Br$, reacts with phenyldichloroarsine in the presence of sodium, and also with phenylarsinebis(magnesium bromide), $Ph{\cdot}As(MgBr)_2$, to give 1 : 2 : 3 : 4-tetrahydro-2-phenyl*iso*arsinoline (as II). Holliman and Mann showed that their reaction when applied to phenyldichlorophosphine gave only traces of the tetrahydro*iso*phosphinoline, which was characterised solely as the crystalline quaternary salt. Later, Holliman and Mann (*J.*, 1947, 1634) developed an alternative synthesis of 2 : 2-disubstituted 1 : 2 : 3 : 4-tetrahydro*iso*phosphinolinium salts: since, however, for the stereochemical purpose of their investigation the 2-substituents were both aryl groups, these


(I.)


(II.)

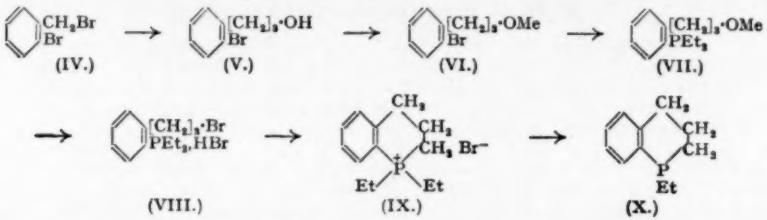

(III.)

compounds did not lend themselves to the preparation of the cyclic tertiary phosphines. The object of the present investigation was therefore to devise practicable syntheses of tertiary phosphines of types (I) and (II).

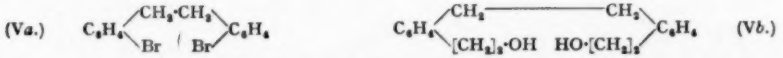
Our initial experiments on the preparation of the phosphinoline showed that an approach similar to that of Burrows and Turner's synthesis of the arsenic analogue was not apparently practicable. The latter workers prepared their methyl-3-phenylpropylchloroarsine by the thermal decomposition of dimethyl-3-phenylpropylarsine dichloride, $Ph{\cdot}[CH_2]_3{\cdot}AsMe_2Cl_2$, involving loss of methyl chloride, a reaction which has subsequently been widely used with other compounds of similar type. We found, however, that the conversion of diethyl-3-phenylpropylphosphine, $Ph{\cdot}[CH_2]_3{\cdot}PEt_2$, into the pure dichloride was difficult (we did not effect it), and the crude dichloride did not undergo the required decomposition; moreover, the crystalline phosphine dibromide, when heated, did not afford the required bromophosphine. It is probable however that if the chlorophosphine, $Ph{\cdot}[CH_2]_3{\cdot}PEtCl$, could be prepared, the desired cyclisation could then be achieved.

An alternative synthesis was therefore developed, which was based essentially on the fact that many quaternary ethylphosphonium chlorides undergo smooth thermal decomposition, an ethyl group breaking off as ethylene with the formation of the tertiary phosphine hydrochloride. This reaction proceeds particularly well when there are two ethyl groups in the phosphonium chloride, but secondary reactions may occur if benzyl or certain other groups are present (Collie, *J.*, 1888, **53**, 714; Meisenheimer *et al.*, *Annalen*, 1926, **449**, 213). The starting material of our successful synthesis was *o*-bromobenzyl bromide (IV), prepared by Holliman and Mann's modification (*loc. cit.*) of Kenner and Wilson's method (*J.*, 1927, 1110). This bromide, when suitably treated with one atomic proportion of magnesium, gave *o*-bromobenzylmagnesium bromide, which then reacted with ethylene oxide to give 3-*o*-bromophenylpropan-1-ol (V). The successful preparation and manipulation of this Grignard reagent required considerable care. The preparation was carried out under an atmosphere of nitrogen, otherwise oxidation readily occurred with the subsequent formation of *o*-bromobenzyl alcohol. Moreover a number of side reactions occurred, and among the by-products were identified

2 : 2′-dibromodibenzyl (V*a*) and 2 : 2′-di-(2-hydroxyethyl)dibenzyl (V*b*), while a low-boiling fraction which was apparently ethylene bromohydrin was also obtained. Since however the required propanol (V) was obtained in 47% yield, the method was satisfactory. The propanol

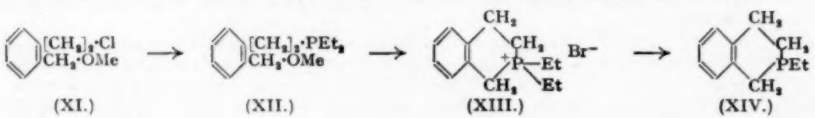


(V) was then converted by phosphorus tribromide into the corresponding bromide, which on treatment with sodium methoxide gave 3-*o*-bromophenylpropyl methyl ether (VI). The bromine atom in this compound does not react readily with magnesium; a Grignard reagent was however successfully prepared by the entrainment method, *i.e.*, by treating an ethereal mixture of the bromo-ether (VI) and ethyl bromide with specially activated magnesium. Diethylchlorophosphine, prepared by an extension of Kharasch, Jensen, and Weinhouse's tetraethyl-lead method (*J. Org. Chem.*, 1949, **14**, 429), reacted with this Grignard reagent to give diethyl-(*o*-3-methoxypropylphenyl)phosphine (VII), a liquid which was characterised by the preparation of its crystalline methopicrate and its dibromopalladium derivative, $[(C_{14}H_{23}OP)_2PdBr_2]$.



When (VII) in acetic acid was boiled with hydrogen bromide, the methoxy-group was replaced by bromine. There is little doubt, however, that no appreciable cyclisation occurred at this stage, and that the product was almost solely the hydrobromide of *o*-3-bromopropylphenyl-diethylphosphine (VIII), for the residue, after evaporation of the acetic acid, was entirely soluble in water: neutralisation with sodium hydrogen carbonate, however, liberated an oil (the free phosphine) which was extracted with chloroform, in which solvent an exothermic reaction rapidly occurred. This reaction was almost certainly the cyclisation to 1 : 1-diethyl-1 : 2 : 3 : 4-tetrahydrophosphinolinium bromide (IX) which then promptly dissolved in the aqueous layer, leaving the chloroform layer almost solute-free. Addition of sodium picrate solution to this aqueous layer precipitated the phosphinolinium picrate, which after purification was converted by the usual method into the quaternary chloride (as IX).

This chloride without purification was then subjected to thermal decomposition under reduced pressure, whereby a distillate consisting of 1-ethyl-1 : 2 : 3 : 4-tetrahydrophosphinoline (X) and its crystalline hydrochloride was obtained. This mixture ultimately furnished the pure liquid phosphine, b. p. 141—143°/18 mm., in 78% yield, further characterised as the crystalline methiodide, methopicrate, and dibromopalladium derivative, $[(C_{11}H_{15}P)_2PdBr_2]$.



In the *iso*phosphinoline series, our synthesis has been an extension of the earlier work of Holliman and Mann (*loc. cit.*). *o*-2-Chloroethylbenzyl methyl ether (XI) was converted into a Grignard reagent, which with diethylchlorophosphine gave diethyl-2-*o*-methoxymethylphenylethylphosphine (XII). This compound, like its isomeride (VII), was then cyclised by treatment in boiling acetic acid solution with hydrogen bromide. In this case, however, cyclisation to the quaternary phosphonium bromide (XIII) appeared to occur almost immediately after the concentrated acidic solution was neutralised with sodium hydrogen carbonate. The addition of sodium picrate to the aqueous layer then precipitated 2 : 2-diethyl-1 : 2 : 3 : 4-tetrahydro-*iso*phosphinolinium picrate (as XIII). This difference in the two series is not surprising, for

the bromomethyl group formed by the action of the hydrogen bromide on (XII) would be more reactive than the 3-bromopropyl group similarly formed from (VII); moreover the trialkylphosphine group in (XII) would also be more reactive than the aryldialkylphosphine group in (VII).

The quaternary picrate was then converted into the corresponding chloride (as XIII), which on thermal decomposition gave 2-ethyltetrahydro*iso*phosphinoline (XIV), solely however in the form of its hydrochloride, from which the free phosphine, b. p. 129—132°/15 mm., was subsequently obtained. Again, the fact that the decomposition of this quaternary chloride gave only the hydrochloride of the tertiary phosphine, whereas that of the isomeric chloride (as IX) gave a mixture of the free tertiary phosphine and its hydrochloride, is not surprising, for it would be expected that the phosphine group in (XIV) would be both more reactive and more strongly basic than that in the isomeride (X). It was noted moreover that the *iso*phosphinoline (XIV) was considerably more susceptible to aerial oxidation than the phosphinoline (X).

We are now engaged in the detailed investigation of the chemistry of the two phosphines (X) and (XIV), particularly with regard to their possible use in the synthesis of *spiro*cyclic quaternary phosphonium salts. We are also applying similar syntheses to the preparation of 1-substituted phosphindolines and 2-substituted *iso*phosphindolines.

Experimental.

Ethyldichlorophosphine.—The crude dichlorophosphine, obtained in 80% yield by the method of Kharasch *et al.* (*loc. cit.*), was distilled from the reaction flask during 3 hours, and on redistillation gave the pure phosphine, b. p. 111—113° (65%).

Diethylchlorophosphine.—A mixture of the above phosphine (130 g.) and tetraethyl-lead (97 g., 0·3 mol.) was stirred and heated for 36 hours at 140—145° in a nitrogen atmosphere. Distillation of the mixture then gave the crude *monochlorophosphine* (89 g., 70%) which on careful fractionation afforded the pure phosphine, b. p. 131—132° (Found: C, 38·1; H, 7·9. $C_4H_{10}ClP$ requires C, 38·5; H, 8·1%) (47 g., 38%). An earlier fraction, b. p. 125—131° (36 g.), was discarded.

Diethyl-3-phenylpropylphosphine.—3-Phenylpropyl bromide was prepared from the alcohol by the method of Rupe and Burgin (*Ber.*, 1910, **43**, 178). A Grignard reagent, prepared by the action of the bromide (12·4 g.) in ether (40 c.c.) on magnesium (1·55 g.) under nitrogen, was boiled under reflux for 30 minutes, cooled in ice-water and vigorously stirred whilst a solution of diethylchlorophosphine (5·8 g., 0·75 mol.) in benzene (50 c.c.) was added dropwise during 20 minutes. The solution was then boiled for 1·5 hours, cooled, and hydrolysed with saturated aqueous ammonium chloride. The ethereal solution was separated, dried, and distilled (in a nitrogen atmosphere throughout), and furnished the phosphine as a colourless liquid, b. p. 108—109°/0·3 mm. (7·25 g., 75%). It was characterised as its *methiodide*, colourless crystals (from alcohol), m. p. 87—88° (Found: C, 48·4; H, 7·0. $C_{14}H_{24}IP$ requires C, 48·0; H, 6·9%).

When it was desired to convert this phosphine into the phosphine dichloride, considerable difficulty was encountered in finding a solvent which would be unaffected both by the phosphine and by chlorine. The phosphine readily reacted even with cold carbon tetrachloride to give a dark oil, which was presumably the salt $Cl{\cdot}C(PEt_2Cl{\cdot}[CH_2]_3{\cdot}Ph)_3$, comparable to the compound $Cl{\cdot}C(PEt_2Cl)_3$ (Hofmann, *J.*, 1861, 488; Hantzsch and Hibbert, *Ber.*, 1907, **40**, 1516). Consequently, direct union without a solvent was attempted by passing a stream of chlorine greatly diluted with nitrogen over the chilled and agitated phosphine. Even so, the vigorous reaction made quantitatively controlled addition difficult, and subsequent distillation gave no useful product. The addition of bromine (1 mol.) to a chloroform solution of the phosphine followed by evaporation of the solvent gave a solid residue, presumably of the phosphine dibromide, but again destructive distillation gave no well-defined product.

3-o-Bromophenylpropan-1-ol (V).—This preparation was performed throughout in an atmosphere of nitrogen. *o*-Bromobenzyl bromide (160 g.) in ether (500 c.c.) was added dropwise to a stirred mixture of magnesium (16 g., 1·03 mol.) and ether (50 c.c.); after the reaction had been started by the addition of an iodine crystal, the rate of bromide addition was adjusted so that formation of the Grignard reagent proceeded without ebullition of the ether. When the formation of the Grignard reagent had been completed by 2·5 hours' stirring, a solution of ethylene oxide (63 c.c., 2 mols.) in ether (200 c.c.) was slowly added, a sticky solid slowly separating. The mixture, after being set aside overnight, was hydrolysed by dilute sulphuric acid. The ethereal layer, on drying and distillation, gave the fractions: (*a*) b. p. 50°/17 mm. (73 g.), the properties of which indicated that it was ethylene bromohydrin; (*b*) b. p. 110—113°/0·5 mm. (64·5 g.); (*c*) b. p. 113—139°/0·5 mm.; (*d*) b. p. 139—145°/0·5 mm.; and (*e*) b. p. 145—*ca.* 220°/0·5 mm.

Fraction (*b*) was the colourless *propanol* (47% yield), which on refractionation had b. p. 106—108°/0·5 mm. (Found: C, 50·4; H, 5·2. $C_9H_{11}OBr$ requires C, 50·2; H, 5·2%). It gave a 3 : 5-*dinitrobenzoate*, colourless crystals, m. p. 96—97°, from light petroleum (Found: C, 47·2; H, 3·0; N, 6·9. $C_{16}H_{13}O_6N_2Br$ requires C, 46·95; H, 3·2; N, 6·85%). It also reacted with phenyl *iso*cyanate to give *3-o-bromophenylpropyl N-phenylcarbamate*, colourless crystals, m. p. 75·5—76°, from light petroleum (Found: C, 57·7; H, 4·85; N, 4·3. $C_{16}H_{16}O_2NBr$ requires C, 57·5; H, 4·8; N, 4·2%). The structure of the propanol was further confirmed by alkaline permanganate oxidation to *o*-bromobenzoic acid, m. p. 148—149°, alone and mixed.

Fraction (*d*) slowly deposited crystals, which, after repeated crystallisations from alcohol, furnished 2 : 2′-dibromodibenzyl (V*a*), m. p. 84° (Found : C, 49·4; H, 3·7. Calc. for $C_{14}H_{12}Br_2$: C, 49·4; H, 3·6%). Kenner and Wilson (*loc. cit.*) give m. p. 84·5°.

Fraction (*e*), which became semi-solid, was recrystallised repeatedly from *cyclo*hexane, and furnished colourless crystals of 2 : 2′-*di*-(2-*hydroxyethyl*)*dibenzyl* (V*b*), m. p. 98—99° (Found : C, 80·1; H, 8·35. $C_{18}H_{22}O_2$ requires C, 79·95; H, 8·2%).

3-o-*Bromophenylpropyl Bromide*.—This *compound*, prepared by the addition of the propanol to chilled phosphorus tribromide followed by 1 hour's heating at 100°, was obtained in 83% yield as a colourless liquid, b. p. 84—85°/0·3 mm. (Found : C, 38·6; H, 3·4. $C_9H_{10}Br_2$ requires C, 38·9; H, 3·6%).

3-o-*Bromophenylpropyl Methyl Ether* (VI).—This was prepared by the cautious addition of the foregoing compound (120 g.) to a chilled solution of sodium (11 g.) in methyl alcohol (300 c.c.). The product, after 1 hour's boiling, was worked up and gave the *ether* as a colourless liquid, b. p. 127—129°/15 mm. (Found : C, 52·2; H, 5·95. $C_{10}H_{13}OBr$ requires C, 52·4; H, 5·7%) (83 g., 84%).

Diethyl-(o-3-*methoxypropylphenyl*)*phosphine* (VII).—A solution of the ether (VI) (48·4 g.) and ethyl bromide (11·55 g., 0·5 mol.) in ether (150 c.c.) was slowly added to magnesium turnings (8·2 g., 1·58 atoms) which had been previously activated by heating with iodine (Holliman and Mann, *loc. cit.*) and then covered with ether (20 c.c.). The reaction soon started, and the rate of addition of the mixed bromides was then adjusted so that the ether boiled only gently without external cooling. The complete mixture was boiled for 3 hours in a nitrogen atmosphere, cooled, and stirred whilst a solution of diethylchlorophosphine (33 g., 1·25 mols.) in benzene (150 c.c.) was slowly added, and then boiled again for 2 hours. After hydrolysis with ammonium chloride, the usual treatment furnished the *phosphine*, b. p. 155—158°/15 mm. (Found : C, 70·7; H, 9·8. $C_{14}H_{23}OP$ requires C, 70·5; H, 9·7%) (37 g., 73%). The phosphine always frothed vigorously on distillation.

Addition of methyl iodide to an ethereal solution of the phosphine precipitated the methiodide as a gum, an aqueous solution of which, when treated with sodium picrate, gave the *methopicrate*, yellow crystals, m. p. 99—99·5°, from alcohol (Found : C, 52·6; H, 6·0. $C_{21}H_{28}O_8N_3P$ requires C, 52·4; H, 5·9%).

When an acetone solution of the phosphine was mixed with an aqueous solution of potassium palladobromide, yellow crystals of *dibromobis*[*diethyl*-(o-3-*methoxypropylphenyl*)*phosphine*]*palladium* separated; these had m. p. 149·5—150° after recrystallisation from alcohol (Found : C, 45·05; H, 6·25. $C_{28}H_{44}O_2Br_2P_2Pd$ requires C, 45·2; H, 6·2%).

1 : 1-*Diethyl*-1 : 2 : 3 : 4-*tetrahydrophosphinolinium Picrate*.—A stream of dry hydrogen bromide was passed for 3 hours through a solution of the phosphine (VII) (17·5 g.) in a mixture of acetic acid (600 c.c.) and constant-boiling hydrobromic acid (600 c.c.) maintained at 120—130°. The solvent was then distilled off under reduced pressure, and the residue, undoubtedly consisting of the hydrobromide (VIII), dissolved in water. The solution was treated with an excess of sodium hydrogen carbonate, whereupon an oil separated. The addition of chloroform dissolved this oil, and the temperature of the chloroform layer soon rose perceptibly. The mixture was then shaken vigorously, so that the cyclised phosphinolinium bromide (IX) was extracted by the aqueous layer. The latter, when treated with sodium picrate solution, deposited the *phosphinolinium picrate* (28·8 g., 90%) which, once recrystallised from alcohol, formed yellow crystals, m. p. 111—111·5° (Found : C, 52·3; H, 5·2. $C_{19}H_{23}O_7N_4P$ requires C, 52·4; H, 5·1%).

1-*Ethyl*-1 : 2 : 3 : 4-*tetrahydrophosphinoline* (X).—The picrate (29 g.) was converted into the chloride by shaking it with concentrated hydrochloric acid (75 c.c.) and water (75 c.c.), the picric acid being then removed by ether-extraction. After distillation of the water, the residual chloride (which tended to crystallise on cooling, but which was not purified) was heated to 350—370° at 20 mm. pressure. Decomposition occurred smoothly, with the separation of a mixture of the liquid phosphine (X) and its crystalline hydrochloride in the receiver : after 2 hours there was no residue in the distillation flask. The mixture was treated with sodium hydrogen carbonate solution, and the free phosphine extracted with chloroform; distillation subsequently gave the pure *phosphine* (X) as a colourless liquid, b. p. 141—143°/18 mm. (Found : C, 73·7; H, 8·4. $C_{11}H_{15}P$ requires C, 74·1; H, 8·5%) (9·3 g., 78%). The identity of the crystalline hydrochloride in the distillate was shown by the fact that the crystals, after decomposition with sodium hydrogen carbonate, and the liquid phosphine, with potassium palladobromide each gave *dibromobis*-(1-*ethyl*-1 : 2 : 3 : 4-*tetrahydrophosphinoline*)*palladium*, orange crystals (from alcohol), m. p. 153·5—154° (Found : C, 42·4; H, 5·1. $C_{22}H_{30}Br_2P_2Pd$ requires C, 42·4; H, 4·9%).

The phosphine was further characterised by the preparation of the *methiodide*, colourless crystals (from alcohol), m. p. 184—185° (Found : C, 44·7; H, 5·6. $C_{12}H_{18}IP$ requires C, 45·0; H, 5·7%), and the *methopicrate*, yellow crystals (from alcohol), m. p. 121° (Found : C, 51·3; H, 4·9; N, 10·1. $C_{18}H_{20}O_7N_3P$ requires C, 51·3; H, 4·8; N, 10·0%). The ethiodide was also prepared and converted into the ethopicrate, which was shown to be identical with that utilised for the preparation of the phosphinolinium chloride.

Diethyl-2-o-*methoxymethylphenylethylphosphine* (XII).—o-2-Chloroethylbenzyl methyl ether (XI) was prepared according to Holliman and Mann's directions (*loc. cit.*). A Grignard reagent was prepared in a nitrogen atmosphere from a solution of the methyl ether (36 g.) and ethyl bromide (10·8 g., 0·5 mol.) in ether (180 c.c.), and magnesium (7·2 g., 1·5 atoms) covered with ether (20 c.c.). The reaction was started by gentle warming, and the halide solution added with stirring at such a rate as to maintain gentle boiling. The preparation was then precisely as that of the phosphine (VII), with addition, however, of a solution of diethylchlorophosphine (33 g., 1·3 mols.) in benzene (250 c.c.). The *phosphine* (XII), worked up in the usual way, had b. p. 117—118°/0·2 mm. (Found : C, 68·6; H, 9·6. $C_{14}H_{23}OP$ requires C, 70·5; H, 9·7%) (34·5 g., 74%). The very ready aerial oxidation prevented accurate analysis.

The phosphine was characterised by the preparation of the *methiodide*, colourless crystals (from alcohol), m. p. 106·5—107° (Found: C, 47·1; H, 7·15. $C_{13}H_{24}OIP$ requires C, 47·35; H, 6·9%), and the *methopicrate*, yellow crystals (from alcohol), m. p. 66·5—67° (Found: C, 52·6; H, 6·0; N, 8·9. $C_{21}H_{23}O_8N_3P$ requires C, 52·4; H, 5·9; N, 8·7%), and also *dibromobis(diethyl-2-o-methoxymethylphenylethylphosphine)palladium*, orange crystals, m. p. 106·5—107° (Found: C, 45·4; H, 6·4. $C_{32}H_{48}O_2Br_2P_2Pd$ requires C, 45·2; H, 6·2%).

2 : 2-*Diethyl*-1 : 2 : 3 : 4-*tetrahydroisophosphinolinium Picrate*.—This was prepared precisely as the isomeric picrate. After passage of the hydrogen bromide for 2·5 hours, the solvent was removed, and the residual syrup dissolved in water and neutralised with sodium hydrogen carbonate. The aqueous solution was shaken with chloroform, which now, however, underwent no perceptible rise in temperature. The aqueous layer, treated with sodium picrate, gave the *iso*phosphinolinium picrate (7·15 g.). The chloroform layer was boiled and evaporated, and the residue when dissolved in water gave a further crop of the picrate (5·4 g.; total yield, 50%). Recrystallisation from methyl alcohol gave the pure *picrate*, yellow crystals, m. p. 98—98·5° (Found: C, 52·5; H, 5·3; N, 10·0. $C_{19}H_{22}O_7N_4P$ requires C, 52·4; H, 5·1; N, 9·7%).

2-*Ethyl*-1 : 2 : 3 : 4-*tetrahydroisophosphinoline* (XIV).—The picrate was converted into the crude chloride and the latter subjected to thermal decomposition precisely as the earlier isomeric compounds. The distillate consisted apparently solely of the *iso*phosphinoline hydrochloride, which crystallised very readily. Neutralisation with sodium hydrogen carbonate followed by chloroform extraction ultimately gave the iso*phosphinoline* as a colourless liquid, b. p. 129—132°/15 mm. (Found: C, 72·4; H, 8·5. $C_{11}H_{15}P$ requires C, 74·1; H, 8·5%) (yield 78%). The very ready oxidation caused low carbon values on analysis.

The *iso*phosphinoline was characterised by the preparation of the *ethiodide*, colourless crystals (from acetone), m. p. 93—94° (Found: C, 46·3; H, 6·2. $C_{13}H_{20}IP$ requires C, 46·7; H, 6·0%), which was converted into the ethopicrate, identical with that used in the preparation. The phosphine also gave *dibromobis-(2-ethyl*-1 : 2 : 3 : 4-*tetrahydroisophosphinoline)palladium*, deep orange crystals (from alcohol), m. p. 165·5—166° (Found: C, 42·1; H, 5·0. $C_{22}H_{36}Br_2P_2Pd$ requires C, 42·4; H, 4·9%).

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UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, October 27th*, 1950.]

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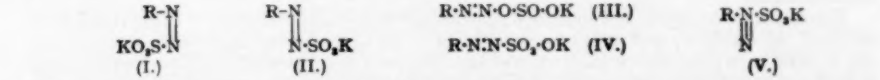
92. *Hantzsch's Isomeric Diazosulphonates.*

By H. C. FREEMAN and R. J. W. LE FÈVRE.

Much of the evidence recorded hitherto on the formulation of the diazosulphonates is inconclusive. Alkali salts of ten pairs (five not previously described) of isomeric diazosulphonic acids have therefore been prepared. Exposure of aqueous solutions to sunlight causes the production of the unstable from the stable forms accompanied by some irreversible decomposition. Thermal changes in the dark proceed in the direction: unstable → stable. Small differences of λ and ε are found between the ultra-violet spectra of the members of each pair. The belief that their absorptions are identical is thus demonstrably incorrect. Attempts to make kinetic and other physical measurements are described. Of the structural (Bamberger, Hodgson; sulphite–sulphonate) and the configurational (Hantzsch; *cis-trans*-sulphonates) explanations for this series of isomers, the latter is preferred.

As is well known (cf. Sidgwick's "Organic Chemistry of Nitrogen," Oxford, 1942, p. 418; Saunders, "The Aromatic Diazo-Compounds and Their Technical Applications," 1949, p. 147), Hantzsch (*Ber.*, 1894, **27**, 1702, 1726, 2099; cf. also Hantzsch and Reddelien, "Die Diazo-Verbindungen," Stuttgart, 1921) regarded the various pairs of isomeric compounds isolable from diazonium salts and alkali sulphites in aqueous solution as cases (with the metallic diazoates



and diazocyanides) where the –N═N– unit may adopt a *cis*- or *trans*-configuration, as indicated by (I) and (II). Acrimonious controversy followed this suggestion. Attack came particularly from Bamberger (*Ber.*, 1894, **27**, 2582, 2930) who—while not disputing the possibility of

geometrical isomerism about the azo-group—supported an explanation already mentioned by Hantzsch himself (*ibid.*, p. 2099), namely, that in these cases the differences are structural, the unstable and stable forms being respectively sulphites (III) and sulphonates (IV). Blomstrand and others (*J. pr. Chem.*, 1896, **53**, 169; 1897, **55**, 481) together with —at one stage—Bamberger (*Ber.*, 1895, **28**, 225, 444) wrote the stable varieties as diazosulphonates (IV) and their labile modifications as (V), but for reasons mentioned by Sidgwick (*op. cit.*, p. XIII; cf. also p. 417) such a formulation is unacceptable to-day

Hantzsch based his views mainly on those properties which appeared common to the three groups of isomeric diazo-compounds [diazocyanides, metallic diazoates, and diazosulphonates]. In each, one form coupled with alkaline solutions of phenols, decomposed with evolution of nitrogen, and was characterised by instability, and in these respects was in contrast to a second form which did not couple and was stable in conditions (*e.g.*, exposure to air, drying, etc.) where the first decomposed. However, Bamberger (*loc. cit.*; *Ber.*, 1895, **28**, 225, 444) and Claus (*J. pr. Chem.*, 1894, **50**, 239) contended that just those differences which distinguished the labile diazo-hydrates, -cyanides, and -sulphonates from their stable isomers, eliminated any probability of geometrical isomerism. In modern terms, these authors thought that mere alteration of bond directions could not be responsible for such great changes in chemical reactivity. Hantzsch (*Ber.*, 1895, **28**, 676) reiterated his original thesis. In a further paper with Schmiedel (*Ber.*, 1897, **30**, 71) he summarised his views. Geometrical isomerism involving N=N linkages, was to him just as real as that with C=C, with the reservation that nitrogen atoms were less reactive than carbon atoms.

Hodgson and Marsden (*J.*, 1943, **470**; cf. also Hodgson and Bailey, *J.*, 1948, 1183) have recently revived Bamberger's suggestion that the relationship is constitutional and not configurational. It is of interest therefore to consider the arguments supporting the sulphite formula.

Hantzsch (*Ber.*, 1894, **27**, 2099) was incorrect in claiming that isomerism of the type $R{\cdot}SO_3K \rightleftharpoons RO{\cdot}SO_2K$ was not found elsewhere. Bamberger (*loc. cit.*) was able to quote many examples to the contrary, and Warlitz had demonstrated a sulphite–sulphonate rearrangement involving C–O ⟶ C–S, but Hantzsch and Schmiedel (*loc. cit.*) denied that this was analogous to $-N_2-O \longrightarrow -N_2-S$.

The labile isomers decolorised iodine and permanganate and gave sulphur dioxide with acids. Bamberger regarded this as conclusively in favour of the sulphite structure. Since, however, the aqueous solution of the isomer did not dissolve silver chloride, he was forced to make the reservation that the compound was actually a " complex sulphite." Hantzsch drew attention to this, and emphasised that it was not made clear why " complex sulphites " differed from ordinary sulphites (*loc. cit.*, 1894, p. 3527). He found, further, that the sulphite reactions were not instantaneous, but delayed, *e.g.*, benzene *syn*-diazosulphonates precipitated barium sulphite only on prolonged storage. In this and other respects these salts were like the double salts of mercury with alkali sulphites—salts shown by Barth (*Z. physikal. Chem.*, 1892, **9**, 195) to be sulphonates and not salts of sulphurous acid; *e.g.*, $Hg(SO_3K)_2$, which exhibited " delayed " sulphite reactions, gave the ions $Hg(SO_3)^-$ and $2K^+$ in solution and was neutral.

Hodgson's recent contributions to the subject (*loc. cit.*; *J.*, 1948, 1096) have been based on the assumption (supported by analogy) that the N–S bond is always more stable than the N–O bond; for instance, it is claimed that Hantzsch's *anti*-diazosulphonate (whose structure is not questioned) retains its N–S bond during the reactions : $Ar{\cdot}N_2{\cdot}SO_3K \longrightarrow Ar{\cdot}N_2{\cdot}SO_3{\cdot}N_2{\cdot}Ar' \longrightarrow Ar{\cdot}N_2{\cdot}SO_3K + (\beta)C_{10}H_7O{\cdot}N_2{\cdot}Ar'$, while the *syn*-diazosulphonate evidently contains the weaker N–O link, since a parallel treatment proceeds : $Ar{\cdot}N_2{\cdot}O{\cdot}SO_2K \longrightarrow Ar{\cdot}N_2{\cdot}O{\cdot}SO_2{\cdot}N_2Ar' \longrightarrow Ar{\cdot}N_2{\cdot}(\beta)C_{10}H_7O$ (where Ar = Ph, Ar′ = *p*-$NO_2{\cdot}C_6H_4$). In fact, some $Ar'{\cdot}N_2{\cdot}(\beta)C_{10}H_7O$ is also isolated, because—in Hodgson's view—the initial *syn*-preparation always contains the *anti*-isomer requisite for the first of the two reactions just written.

Hodgson (*J.*, 1948, 1097) further states that, in general, compounds with $\cdot N_2{\cdot}SR$ bonds (*e.g.*, Ar·N:N·SR, where SR = SMe, SAr′, or SO_2R) will not couple with alkaline β-naphthol, but the *syn*-diazosulphonates do so; hence, it is argued, they do not possess the N–S link, but are diazosulphites.

The relevance of kinetic and spectral data was realised half a century ago. The first measurements of the stabilities and rates of isomerisation of the isomers were made by Bamberger (*loc. cit.*, p. 2930), who used the results to support his allegations that Hantzsch had never investigated or analysed a pure labile compound. The figures which he obtained, from titrations of the excess of iodine in a solution into which he had placed freshly-precipitated labile compound, indeed tended to show a high degree of conversion of the labile into the stable isomer within a matter of minutes of the formation of the sample.

Hantzsch (*loc. cit.*, p. 3527) repeated these experiments, and by suitable corrections of Bamberger's methods showed that his own specimens of *syn*-diazosulphonate were 96% pure. (For instance, Hantzsch mixed his diazo-solution and sulphite solution rapidly, to minimise isomerisation; Bamberger had performed the addition gradually. Hantzsch used N/100-iodine solutions for his estimations, to assist the speedy dissolution and reaction of the labile solid; Bamberger had used N/10-solutions, giving him a smaller volume and hence slower rate of solution and thus of reaction.)

Hantzsch and Schmiedel (*loc. cit.*) continued these analyses, and also used the same procedure to follow the speeds of isomerisation with alkyl- and halogen-substituted benzene derivatives. Qualitative observations were also found practicable by naphthol-coupling. The results indicated that alkyl and nitro-substituents increased the velocity; halogen substituents had the reverse effect. The darker the colour of the *syn*-form, the greater its instability seemed to be. The isomerisation, it should be noted, appeared not to be a first-order process.

Despite Hantzsch's measurements of the decomposition rates of his labile isomers, and the recorded high purity of his specimens, Hodgson and Marsden have concluded that the "*syn*"-compound is "always mixed with the *anti*-isomeride, into which it passes rapidly." This assertion, repeated in Hodgson's 1948 papers, is based on reactions similar to those just mentioned.

Hantzsch early pointed out (1894) that both the labile and the stable isomers of the diazosulphonates were coloured, the labile member of each pair having the deeper colour, yet all diazonium salts of colourless anions were colourless; this meant that the diazosulphonates could not be salts of SO_3^{--}. Bamberger (*loc. cit.*, p. 2930) at once objected on the grounds that the colour of the diazosulphonates, with N:N·S, could not be compared with that of other diazo-compounds, such as the cyanides, with N:N·C. In any case, he wrote, the relation between colour and chemical structure was still too little known to be used as an argument; *e.g.*, the yellow lead iodide and the colourless potassium iodide were "analog constituirt und dennoch optisch verschieden." Hantzsch (1894) at once retorted that Bamberger had referred to the solid iodides; their *solutions* were both colourless. He continued with a description of cryoscopic measurements, which showed that *both* the *syn*- and the *anti*-diazosulphonates were dissociated into *two* ions. Hence any formulæ which *necessitated* dissociation into three ions, *viz.*, $Ar{\cdot}N_2^+$, SO_3^{--}, and K^+, could be excluded. This was taken as evidence against the sulphite formula. Incidentally, the occurrence of only two ions formally disposes of the Blomstrand–Strecker–Erlenmeyer "phenylazonium" structure (V) for the labile isomer: according to modern theory, (V) can be modified only to $Ar{\cdot}\overset{+}{N}{:}N\ SO_3^{--}\ K^+$, a diazonium salt with three ions.

Finally, Dobbie and Tinkler (*J.*, 1905, **87**, 273) and Hantzsch and Lifschitz (*Ber.*, 1912, **45**, 3011) have produced spectroscopic data favouring the structural identity hypotheses. The graphs in the second paper (the earlier measurements were less accurate and more restricted in range) particularly, show the similarities between the ultra-violet and the visible absorption bands of diazosulphonate pairs

This spectroscopic evidence remained unchallenged until recently. Hodgson *et al.* maintain that it is anomalous for compounds of distinctly different colours, chemical stabilities, and energy contents to give almost identical absorption spectra. This is actually a modern variation of Bamberger's theme—that compounds so different could not be geometrical isomers. Further, Hodgson argues that the depth of colour in the diazosulphonates is in reverse order to that in the diazocyanides, *viz.*, in the sulphonates the labile isomer, but in the cyanides the stable isomer has the deeper colour. This, it is claimed, destroys the analogy between the two groups of compounds.

As already mentioned, Hodgson and Marsden (1943) have concluded that the labile forms are always accompanied by a variable proportion of the *anti*-isomers. For this reason, Hodgson's diagnosis that Hantzsch's absorption spectra were identical because they were spectra of the same material, namely, the stable isomer, cannot be dismissed, since it is clear that a considerable fraction of the labile isomer might have isomerised in the time required for the older techniques of absorption spectroscopy available to Hantzsch and his collaborators.

Present Work.—At the outset, therefore, it seemed to us that the formulation of the diazosulphonates still remained a problem lacking sufficient *agreed* observational data for its resolution. We decided accordingly: (*a*) to prepare representative examples of this class, (*b*) to note their behaviour towards daylight, (*c*) to investigate the similarities of ultra-violet and visual spectra recorded for various of these isomers, and (*d*) to seek any measurable differences in properties between the aqueous solutions of the forms, and if possible thereby to study the rates of inversion and attempt to ascertain the energies of activation involved.

(*a*) *Isomers Examined.*—The following diazosulphonates have been prepared during the present investigation:

Diazosulphonic acid.	Forms isolated.
Benzene-	K and Na salts
o-Chlorobenzene-	Free acid, Na, K, and Ag salts
p- ,,	K and Na salts
o-Iodobenzene-	K salts
p- ,,	K salts
2 : 4-Di-iodobenzene-	K salts
2 : 4 : 6-Tribromobenzene-	K salt (one form only)
p-Nitrobenzene-	K salt (one form only)
Diphenyl-2-	K salts
,, -4-	K salts
Diphenyl-4 : 4′-bis-	K salts

No signs of the third, theoretically possible, variety of the diphenylbisdiazosulphonates have been obtained (compare Brown, Le Fèvre, and Whittem, *J.*, 1950, 185).

Five of the above pairs do not appear in the literature. Labile forms are known for at least 12 of the following 46 diazosulphonates, whose parental types include: Benzene (27 examples; Hantzsch *et al.*, *loc. cit.*; Riedel, " Friedländer," **3**, 922; Fischer and Kuzel, *Annalen*, 1883, **221**, 274; Altschul, *Ber.*, 1892, **25**, 1843; Stollé, *Ber.*, 1912, **45**, 2680; Franzen and Schmidt, *J. pr. Chem.*, 1917, **96**, 15; Perkin and Rubinstein, *J.*, 1926, 357; Hall and Gibbs, *J. Amer. Chem. Soc.*, 1927, **49**, 433; Desai, Mehta, and Thosar, *J. Soc. Dyers Col.*, 1938, **54**, 371), naphthalene (4 examples; Hantzsch and Schmiedel, *Ber.*, 1897, **30**, 80; Bamberger, Böcking, and Kraus, *J. pr. Chem.*, 1923, **105**, 251; Hodgson and Bailey, *J.*, 1948, 1183), diphenylamine (3 examples; Zitscher and Seidenfaden, U.S.P. 1,897,410), azobenzene (1 example; Tröger and Puttkammer, *Ber.*, 1907, **40**, 209), and benzeneazonaphthalene (11 examples; Tröger *et al.*, *Arch. Pharm.*, 1917, **255**, 1; *J. pr. Chem.*, 1926, **113**, 268; 1927, **114**, 269). Other examples occur in the technical literature.

In general, the behaviour of the various diazosulphonates was found to correspond to that expected from the literature. The decomposability of the labile isomers varied; for example, the *p*-nitrobenzene derivative began to deteriorate even on the filter-paper, while the halogenated or diphenyl compounds could be kept overnight on a porous tile in a dark vacuum desiccator at 0° with little or no decomposition.

Rough qualitative tests were carried out by means of naphthol coupling to determine the relative rates of isomerisation of the labile into the stable forms. The halogenated benzene derivatives were found to isomerise with rates of approximately the same order, *e.g.*, 1% solutions of the labile *o*-chloro-, *o*-iodo-, and *p*-iodo-benzenediazosulphonates failed to couple with alkaline β-naphthol after 2, 3, and 1 hours at 25°, respectively. It was noted, in anticipation of some spectroscopic observations to be mentioned later, that a solution of the labile *o*-chlorobenzene derivative, when kept at 0°, still coupled strongly after 3 hours.

Since good storage quality of labile isomer seems generally to be accompanied by slow rate of isomerisation (*Ber.*, 1897, **30**, 71), it was surprising to find that the relatively permanent diphenyldiazosulphonates isomerised extremely rapidly, all naphthol coupling of a 2% solution of each of them ceasing within 10 minutes of dissolution; the bisdiazosulphonate gave a heavy precipitate of the *anti*-isomer on standing for this short period.

The observations reported in the early papers of Hantzsch and Bamberger having thus been submitted to a brief confirmatory review, with extension of their experiments to a number of new compounds, some attention was paid to the more recent evidence submitted by Hodgson and Marsden (1943). In particular, it was desired to repeat these authors' preparations of complexes derived from *syn*- and *anti*-diazosulphonates and diazotised amines, since the quantitative data of their paper seemed incomplete. (For instance, no indication is given of the *yield* of complex in any of the five reactions with which Hodgson and Marsden deal.) It was found impossible, however, to carry out the necessary estimations, owing to the instability of the complex formed; *e.g.*, that from *o*-chlorobenzene-*syn*-diazosulphonate and diazotised *p*-nitroaniline decomposed vigorously—even on being sucked semi-dry on the filter-paper—in a manner reminiscent of the more unstable of the labile diazosulphonates.

Despite the fact that Hodgson and Marsden place great reliance both on naphthol coupling and on diazonium-complex formation as showing the extremely rapid transformation of labile into stable isomerides, their recorded proportion of *anti*-isomer in a fresh sample of the labile modification (" 78% being a typical amount " of *anti*-isomer in a fresh, unwashed preparation)

seems very large when compared with the results of Hantzsch and Schmiedel's parallel experiments (*Ber.*, 1897, **30**, 71) using iodometric titrations of the *syn*-form. It is therefore to be regretted that Hodgson *et al.* do not record the relative quantities of the isomers as found, *e.g.*, by estimation of the naphthol-coupling products from the complex of benzene-*syn*-diazosulphonate with diazotised *p*-nitroaniline. In any case, there is no evidence that this complex itself does not isomerise, and that the conclusions drawn from its heterogeneous composition do not in fact relate at least partly to processes taking place *after* the formation of the complex.

A further criticism may be levelled against this work, particularly in view of the unassailability which Hodgson has claimed for the deductions made from it (cf. *J. Soc. Dyers Col.*, 1943, **59**, 271). The formation of the diazosulphonate–diazonium salt complexes was limited—by the instability of most of them—to those derived from the *syn*-diazosulphonates from aniline and *p*-nitroaniline. The use of these substances as test compounds is unfortunate, inasmuch as Hantzsch and Schmiedel reported that the *p*-nitroaniline derivative (whose decomposability we have already noted above) was even more unstable than that from aniline. Hantzsch, in 1894 (*Ber.*, **27**, 3527) as well as in his later paper with Schmiedel and in his spectroscopic observations with Lifschitz (*Ber.*, 1912, **45**, 3011), chose, *e.g.*, the halogen-substituted benzenediazosulphonates as more amenable to experiment than the unsubstituted compound.

In the work to be described below, the relatively stable *o*-chloroaniline derivatives have been used.

(*b*) *Effect of Light on Diazosulphonates.*—It has been known for 60 years (Feer, D.R.-P. 53,455, 1889; " Friedländer," **2**, 558) that diazosulphonates undergo changes on exposure to light, and become capable of coupling with phenols. Feer's work, however, was directed towards photographic applications; moreover, it took place before the discovery of isomerism among diazo-compounds.

Desai, Mehta, and Thosar (*J. Soc. Dyers Col.*, 1938, **54**, 371) regarded the process occurring when stable diazosulphonates were exposed to light as a production of the *syn*-isomers. Their measurements—intended also to determine the rates of conversion—were carried out by iodometric titrations, weighing an azo-compound formed on naphthol coupling, and by periodic observations of pH. References to their results will be made below.

The behaviour of diazosulphonates in light has a bearing also on the theoretical problem of their isomerism. If the isomerism is geometrical, then interconversion of the isomers in light will not be unexpected; if the isomers are related as sulphite to sulphonate, then no equivalent photochemical transformation would appear to have been discovered, and the effect of light—if any—might be a decomposition of the stable isomer.

Photochemical transformations of *cis-trans*-isomers are well-known. *trans*-Stilbene is converted into the *cis*-isomer (Smakula, *Z. physikal. Chem.*, 1934, *B*, **25**, 90; cf. Rollefson and Burton, " Photochemistry and the Mechanism of Chemical Reactions," Prentice-Hall, 1939, 248), *trans*-azobenzene gives a photochemical equilibrium mixture with the *cis*-form (*J.*, 1938, 633), and a similar equilibration has been found for the diazocyanides (*J.*, 1938, 633, 1796, 1878). These cases are of interest in the present instance, since we believe their geometrical isomerism to be established, and since they possibly have in common a non-planar configuration for their less stable isomers (see p. 426).

For the diazocyanides, Stephenson and Waters (*J.*, 1939, 1796) and others (cf. *Chem. and Ind.*, 1948, 158, 432, 732, 782) have concluded that (i) stable diazocyanides are converted photochemically and reversibly into their labile forms; (ii) unstable diazocyanides in alcoholic solution are in tautomeric equilibrium with diazonium cyanides—since silver cyanide is rapidly precipitated with silver nitrate—and (iii) that neutral solutions of the labile varieties give self-coupling products, consequent upon apparent hydrolyses during which hydrogen cyanide is liberated. It is obvious that, if a similar reversible photochemical change can be shown for the diazosulphonates, the case for the analogy between the two types of isomers will be strengthened.

As to (i), during the course of the present experiments, indications were obtained that the process investigated by Desai *et al.* is in fact reversible, with the reservation (cf. iii, below) that complications are introduced by the great decomposability of the labile isomers; and as to (ii), aqueous solutions of the unstable diazosulphonates with silver nitrate do give precipitates of silver sulphite.

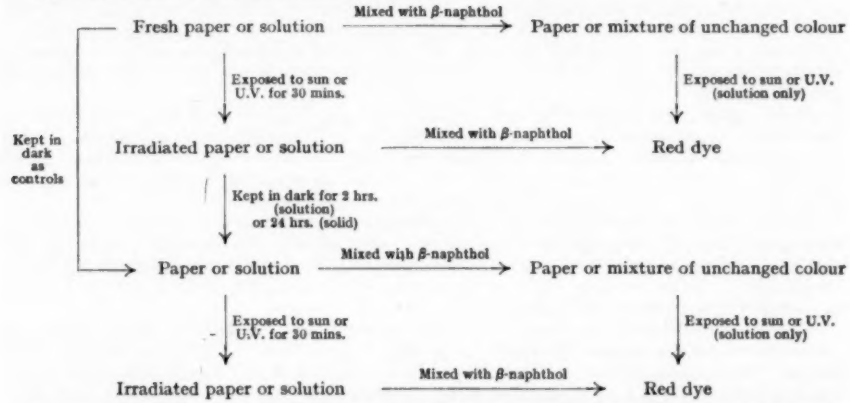
Thus, naphthol coupling being used to show the presence or absence of a labile isomer in solution, a solution of potassium or sodium *o*-chlorobenzene-*anti*-diazosulphonate—which initially did not react with alkaline β-naphthol—was divided, part being kept in the dark for reference. On exposure to sunlight or ultra-violet light for 15—30 minutes, the diazosulphonate solution gave a distinct red colour with the naphthol. A sample of the irradiated solution not

used for the coupling, if left in the dark for some hours, gradually lost its power to couple. On re-irradiation, coupling products could again be obtained; and so on.

Similarly, in repetition of the work of Desai and his co-workers, the diazosulphonate and naphthol solutions were mixed before irradiation, and the precipitation, after 10—15 minutes, of a red dye was observed. Simultaneously with all these experiments, control tests were conducted with solutions in darkened test-tubes; in no case was coupling observed with an unirradiated solution, while it could always be observed after exposure to light.

A parallel series of tests was conducted with the solid *anti*-diazosulphonate : filter-papers were soaked in a solution of *anti*-salt, and dried in an oven. The test for *syn*-isomer was performed by placing a drop of alkaline β-naphthol solution on the paper. In the case of papers which had not been exposed to strong light, or which had lain in a dark place for some hours, no red coloration was obtained. Papers exposed to sun or ultra-violet light gave a strong red colour. In this case, too, blanks were run, *e.g.*, half of each paper was masked with black paper during the irradiation, and tested with naphthol at the same time as the irradiated half. Reversibility of the reaction was shown as in the case of the solution experiments, the only apparent difference between the solid and the solution reactions being the comparative slowness of recovery of the former—24 hours was the order of magnitude of the time required for an irradiated paper to lose its coupling ability, compared with 2 hours for the solution.

These observations may be summarised as below :


Fresh paper or solution
Mixed with β-naphthol
Paper or mixture of unchanged colour
Exposed to sun or U.V. for 30 mins.
Exposed to sun or U.V. (solution only)
Kept in dark as controls
Irradiated paper or solution
Mixed with β-naphthol
Red dye
Kept in dark for 2 hrs. (solution) or 24 hrs. (solid)
Paper or solution
Mixed with β-naphthol
Paper or mixture of unchanged colour
Exposed to sun or U.V. for 30 mins.
Exposed to sun or U.V. (solution only)
Irradiated paper or solution
Mixed with β-naphthol
Red dye

The various attempts to find measurable differences in properties between the isomeric diazosulphonates were accompanied by parallel measurements on irradiated solutions of the *anti*-isomer. The details of these attempts, which were largely unsuccessful, are given on p. 423. At this stage the most relevant measurements were those of the pH of solutions before and after irradiation.

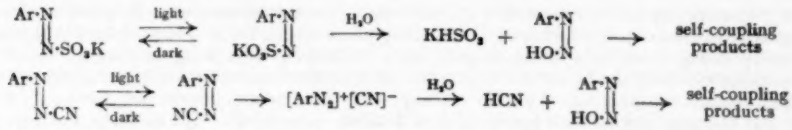
Desai *et al.* (*loc. cit.*) carried out the first measurements of pH of irradiated solutions, and found the pH to fall during irradiation; *e.g.*, a M/200-solution of *o*-chlorobenzene-*anti*-diazosulphonate of original pH 6·02 assumed a nearly constant pH of 2·5 after 90 minutes' irradiation by sunlight. This change was attributed to hydrolytic dissociation of the *syn*-compound. Although we have verified these results, the above explanation cannot be accepted; for, as reported on p. 423, the fresh *syn*-compound did not show a correspondingly lower pH than the pure *anti*-compound, the pH of an isomerising solution remaining approximately constant.

The following is a typical set of our observations : the pH of a solution of *o*-chlorobenzene-*anti*-diazosulphonate, measured before and after irradiation, showed a decrease in pH; after the cessation of illumination, however, a return to the original pH did not occur; instead, the pH decreased further for a certain period of time, until it finally became constant. On further irradiation another decrease in pH was observed.

At the same time, a smell of sulphur dioxide was noticed during and after every irradiation. These two facts—the fall in pH and liberation of sulphur dioxide—seem most easily explained along the lines proposed by Stephenson and Waters (*loc. cit.*) for the diazocyanides, with the exception that—since a form $[RN_2]^+[SO_3K]^-$ is unlikely—no analogue of the diazonium cyanide

intervenes as such, but the alkali sulphonate proceeds to suffer irreversible hydrolysis of the type which Raschig's potassium hydrazinodisulphonate (prepared from chlorosulphonic acid, pyridine, and hydrazine sulphate) underwent when treated with alkali-lye : $N_2H_2(SO_3{\cdot}OK)_2 + 2KOH \longrightarrow N_2 + 2K_2SO_3 + 2H_2O$. It is notable that, in this case, Raschig obtained no nitrogen or sulphite at ice temperatures, when—he suggested—dihydroxyhydrazine was present as an unstable intermediate (for references, see Mellor, " Comprehensive Treatise on Inorganic and Theoretical Chemistry," Longmans, Green & Co., 1928, VIII, pp. 682, 683).

We therefore propose the following scheme, written for comparison above that of Stephenson and Waters for the diazocyanides :—



In this way the fall in pH during illumination appears to be due to the decomposition following hydrolytic dissociation.

Further, the steady decomposition of the *syn*-isomer in photo-equilibrium with the stable form is implicit in the results of Desai *et al.*, who found that the proportion of *syn*-isomer in a continuously illuminated solution reached a maximum, then decreased. It appears that the proportion of *syn-* relative to *anti-* may not have changed, but that the total quantity of

FIG. 1.

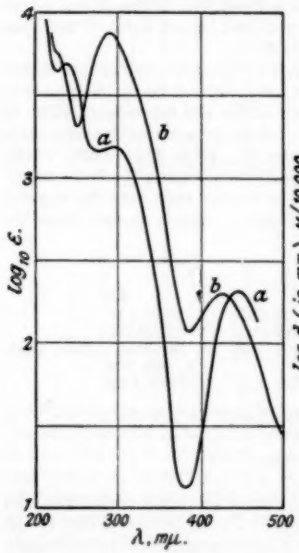


FIG. 2.

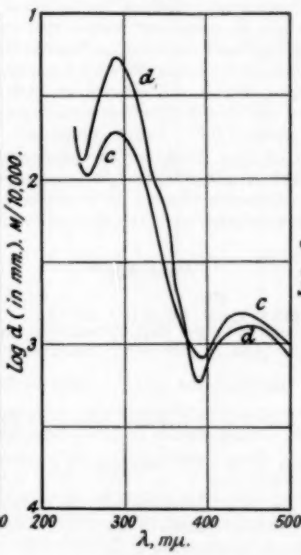
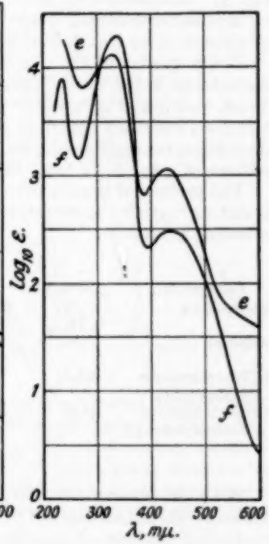


FIG. 3.



(undecomposed) diazosulphonate may have decreased. Only by having the naphthol present in the solution during irradiation were the Indian authors able to obtain a steady increase in the amount of azo-compound precipitated; this experiment, however, involved continuous removal of the *syn*-isomer as it was formed.

As an adjunct to the general investigation of these photochemical reactions, the behaviour of the free *o*-chlorobenzenediazosulphonic acid was examined. This substance, in aqueous solution, decomposed at once on being irradiated, and no evidence of a second isomer could be obtained. It is mentioned here because the evolution of sulphur dioxide during its decomposition parallels the same process in the decomposition of the labile sodium salt.

(*c*) *Ultra-violet and Visible Absorption Spectra.*—Hodgson *et al.* have attacked the spectroscopic evidence produced by Dobbie and Tinkler (*J.*, 1905, **87**, 273) and Hantzsch and Lifschitz (*Ber.*, 1912, **45**, 3011) from both the technical and the theoretical points of view. In particular, they consider it unreliable because the solutions used for the absorption spectra of the labile diazosulphonates were not tested at the end of the measurements to prove that transformation of the *anti*-diazosulphonates had not taken place. From our own experience we admit at once that Hantzsch's spectrum of, *e.g.*, what he thought was *o*-chlorobenzene-*syn*-diazosulphonate must have been that of a mixture of the two isomers. Accordingly, it seemed desirable that any re-examination of the diazosulphonate question should include a repetition of the spectroscopic work.

The absorptions of *o*-chlorobenzene-*syn*- and -*anti*-diazosulphonates were therefore recorded, by means of a Beckman Photoelectric Spectrophotometer, model DU. They are shown diagrammatically in Fig. 1, curves *a* and *b*, respectively. In keeping with Hodgson's suggestions, two precautions were taken. To prevent or, at least, to minimise the isomerisation during the process of spectroscopic examination, the freshly precipitated *syn*-diazosulphonate was dissolved (after brief but thorough drying on a porous tile) in distilled water at 0°. The solution was kept in an ice-bath, and for each point on the absorption curve the spectrophotometer cell was filled with fresh solution from the bulk. The process of filling the cell, replacing it in the instrument, and taking the reading took about 30 seconds. To confirm that the spectrum obtained was indeed that of the labile isomer, reference was made to naphthol-coupling experiments (see above) with a solution kept under similar conditions.

Although the spectra of the two isomers show quite clearly that the compounds are different, yet they show equally clearly the similarity to which Hodgson has taken exception. In Fig. 2, curves *c* and *d*, Hantzsch and Lifschitz's spectra have been redrawn on a similar scale to those of Fig. 1. Comparison of the two figures indicates the inherent correctness of the earlier curve for the *anti*-isomeride; curve *c* is in agreement with a spectrum (not shown here) of the *syn*-solution used for Fig. 1 after it had been kept for one hour at 2—5°.

If the spectra of Fig. 1 are further compared with the absorption spectra of isomers whose geometrical isomerism is highly probable, the general similarity throughout becomes apparent. As an example, the spectra of the two *p*-chlorobenzenediazocyanides are reproduced (Fig. 3) from Le Fèvre and Wilson (*J.*, 1949, 1106). Other compounds, whose geometrical isomers show absorption curves reminiscent of Figs. 1—3, include azobenzene (*J.*, 1938, 431; 1939, 1316), stilbene (*Z. physikal. Chem.*, 1931, *A*, **155**, 353) and (in some respects) the oximes (*J.*, 1933, 1037).

The feature of these pairs of spectra which is most striking is that in each case the isomers absorb at roughly the same wave-lengths but with different intensities. This is evident from the following summary:

Compound.	Solvent.	Absorption * of: *cis*-.	*trans*-.	Ref.
Azobenzene	C_6H_6	430 (3·1), *ca.* 300 (3·6)	450 (2·7), 330 (4·3)	*J.*, 1938, 431.
	$CHCl_3$	438 (3·1), 324 (4·2)	445 (2·5), 319 (4·3)	*J.*, 1939, 1316.
Stilbene	C_6H_6	280 (3·5), *ca.* 220 (3·7)	264 (3·8), 226 (3·5)	*Z. physikal. Chem.*, 1931, *A*, **155**, 353.
p-Chlorobenzenediazocyanide	Et_2O	432 (3·1), 330 (4·1)	438 (2·5), 338 (4·3)	*J.*, 1949, 1106.
o-Chlorobenzenediazosulphonate	H_2O	448 (2·3), 300 (3·2), 238 (3·7)	428 (2·3), 292 (3·9), 228 (3·8)	

* $\lambda_{max.}$ in mμ., and $\log_{10}\varepsilon_{max.}$ (in parentheses).

With the information just recorded we were able to obtain more evidence concerning the nature of the photochemical process discussed in Section (*b*) above. Owing to the lability of the irradiation product, an accurate determination of the spectrum after illumination was not made, since it was thought that what was required was an indication of the *changes* caused by irradiation. Accordingly, the solutions of *anti*-isomer were irradiated for varying periods, and after each the spectrum was quickly scanned (observations of the absorption curves were made at 50 or 100 mμ. intervals, the solutions were briefly re-illuminated, and another set of observations was made, starting at the opposite end of the absorption curves).

The curves in Fig. 4 were obtained by examining a solution (M/5000) of the *anti*-isomer of *o*-chlorobenzenediazosulphonate after 10 (curve *b*), 20 (curve *c*), and 45 (curve *d*) minutes' irradiation at 50 cm. from a mercury-vapour lamp. The solution was the same as that used for the curves in Fig. 1, and the absorption curve of the unirradiated solution is represented in Fig. 4 by curve *a* (broken line). The following comments can be made:

Curve b. Irradiation for 10 minutes has caused a change of absorption in the direction to be expected for a conversion of the *anti*- into the *syn*-isomer (cf. curve *a*, Fig. 1). The absorption at 290 mμ. has decreased in extinction value, while the extinction at 250 mμ. has shown an increase.

Curve c. After 20 minutes, there has been a reversal of the trend at 250 mμ.—the extinction has returned almost to its original value—while the band at 290 mμ. has widened considerably; a new band appears at 275 mμ., and the 300 mμ. band of the *syn*-diazosulphonate spectrum is evident.

Curve d. After 45 minutes, the original spectrum has disappeared; one band only is apparent (the band at 420 mμ. having also disappeared, although not shown in this figure).

Observations on the re-conversion of the *syn*- into the *anti*-isomer were next attempted, each of the above solutions being re-examined after 24 hours, during which they were not exposed to light. As an example of the type of result, Fig. 5 shows the spectrum of a solution exposed for 20 minutes to sunlight (curve *c*); the absorption of the " recovered " solution is shown in curve *f*.

FIG. 4.

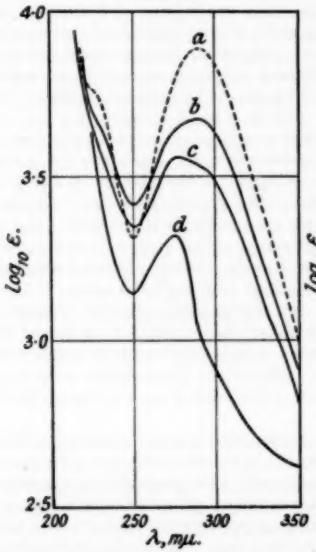
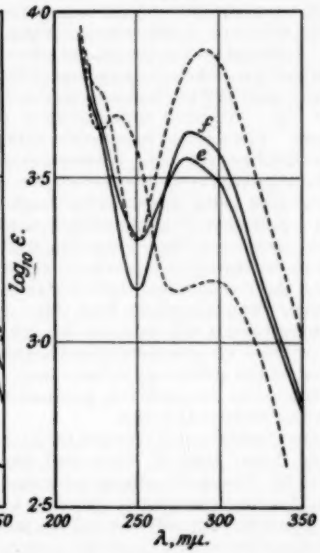


FIG. 5.



In addition, the absorptions of the *syn*- and the *anti*-isomers have been reproduced (broken lines). The resemblance, except for a slight widening of the main band, between curve *f* and the curve of the *anti*-diazosulphonate is apparent; the lowering of the extinction value, which is approximately uniform along the whole curve, is in agreement with the postulated partial decomposition of the irradiation product. Further, a solution irradiated for 10 minutes showed an even greater recovery of its original properties; while one irradiated for 45 minutes displayed an extremely small tendency towards recovery.

From the spectroscopic evidence, as well as from the known reactions of the labile diazosulphonates, it seems not unreasonable to claim that the analogy between the diazocyanides and sulphonates extends beyond spectral details and obvious chemical relationships. In each case the isomers seem not only to be related similarly, but are interconvertible in a fashion common to both; moreover, the labile isomer may undergo hydrolysis and subsequent decomposition. The likelihood of the photo-reaction's being *only* a decomposition—occurring possibly in the surface layer of the solution—seems to be remote, since the spectroscopic evidence shows that *some* return to the original composition does take place.

(*d*) *Miscellaneous Physical Properties of the Isomers.*—The *cis*-isomers both of azobenzene and of the diazocyanides are the denser form (*J.*, 1938, 431; 1939, 531; 1947, 445; 1949, 333).

Since preliminary experiments by naphthol coupling had shown the speed of interconversion of the diazosulphonates to be high, direct density determinations on solutions of the labile and stable salts were not attempted; instead, however, the dilatometric technique found convenient by Le Fèvre and Northcott (*J.*, 1949, 2235) was applied. Although reproducible results were difficult to obtain, the density differences between isomers were evidently small, since no marked change of volume was observed during the spontaneous isomerisations.

Observations of pH were made in the hope that they would either reveal a difference in structure between the isomers or provide a means of following the interconversion rates. Solutions of the separate isomers were not examined, but in order to ensure that the concentrations of the species being compared were equal, measurements were always started on the labile variety, and followed through during the isomerisation process.

Solutions of about 1% concentration and a Leeds and Northrup pH meter being used, no significant changes in pH were noted during the isomerisation (as stated above however, a fully isomerised solution *did* show a distinct fall in pH when irradiated. The cause in these circumstances cannot therefore be the interconversion of the isomers, and our deduction that decomposition as well as interconversion occurs, is supported).

Behind these experiments was the expectation that the degrees of hydrolysis, and therefore the pH's of the solutions of the related sodium salts, would depend on the strengths of their parent acids. Information concerning the relative strengths of sulphurous and sulphonic acids appears to be lacking, although in general sulphonic acids are strong acids, with dissociation constants greater than 10^{-1} (Branch and Calvin " Theory of Organic Chemistry," Prentice-Hall, 1941, Chapter XI). We have been unable to find any measurements for the corresponding sulphurous acids. The relation between the acid strengths of geometrical isomers has, however, received some attention (*op. cit.*). Often a *cis*-carboxylic acid isomer has the greater strength, but this is not unequivocally so, the dissociation constants of the isomers of, *e.g.*, 2-methylbut-1-ene-1-carboxylic acid being approximately equal. We doubt, therefore, whether we should have expected a difference if the diazosulphonates are geometrical isomers. The presumption, however, is that, were one of them a sulphite, this fact would have affected our pH measurement.

In parallel to the tests just mentioned, we have examined the conductivities of isomerising solutions, using the conventional A.C. bridge method (see, *e.g.*, Glasstone, " Introduction to Electrochemistry," Van Nostrand, 1942, 35). No reproducible changes of conductivity were recorded; in some cases a rise occurred, but continued far longer (3·5—4 hours) than the time known to be required for complete isomerisation. Similar increases in conductivity resulted from irradiation of the stable salt in solutions. Since these phenomena were also noted *after* cessation of illumination (occasionally, production of bubbles of gas on the electrodes was seen) they were ascribed to decomposition.

In view of the sensitivity of Blake's radio-frequency conductivity apparatus (*Chem. and Ind.*, 1946, 48; *J. Sci. Instr.*, 1945, 22, 174; 1947, 24, 77, 101) several diazosulphonate solutions, as well as some of the free *o*-chlorobenzenediazosulphonic acid, prepared *via* the silver salt, were examined by it, but no clearer indications than by ordinary procedures were obtained.

The above experience left only one possible method (spectrophotometry) with which to study the kinetics of the spontaneous (thermal) interconversions. Absorption measurements against time at a single wave-length of several isomerising solutions were therefore made. In no case were the data obtained compatible with first-order equations—a conclusion in agreement with the findings, *via* the iodine titration technique, of Hantzsch and Schmiedel (*Ber.*, 1897, 30, 71), and not unexpected if labile diazosulphonates are in fact capable of simultaneous rearrangement and decomposition.

Conclusions.—The following statements may be based upon the above evidence from experiment: (1) The absorption spectra of isomeric diazosulphonates show similarities and differences of the same type and degree as do those of related diazocyanides, azobenzenes, etc. (2) On exposure of the stable diazosulphonates—either as solids or aqueous solutions—to ultra-violet or sun-light, at least partial conversion into the labile form occurs. (3) This interconversion is reversible, the degree of recovery of an irradiated solution towards its original state being reduced by slow decomposition of the labile isomer, the chemical decomposability of which seems to be increased by light. (4) Between aqueous solutions of members of a given pair there are no notable differences of density, pH, or conductivity.

The above points, in general, add to the analogies between diazo-compounds and a number of non-azo-molecules whose geometrical relationship is not in dispute. No instance of a reversible photochemical " sulphonate to sulphite " rearrangement has yet been observed, although the *decomposing* action of light on aqueous diazonium compounds has often been

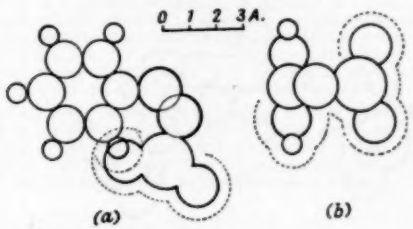
noticed (cf. De Jonge, Dijkstra, and Braun, *Rec. Trav. Chim.*, 1948, **67**, 328; 1949, **68**, 430, for some recent examples). For these reasons we prefer Hantzsch's configurational explanation to Bamberger and Hodgson's structural one.

Configuration and Reactivity.—We now refer to the differences of reactivity between the pairs of compounds which we consider to be geometrically related. In an earlier paper (*J.*, 1947, 445) similar instances from oxime chemistry were cited. Two other examples that appear relevant are: (*a*) that *cis*-stilbene is decomposed without rearrangement to yield unidentified products, under conditions where the *trans*-isomer is unaffected (Smakula, *Z. physikal. Chem.*, 1934, *B*, **25**, 90; cf. Rollefson and Burton, *op. cit.*, p. 248), and (*b*) that *cis*-azobenzene with 10N-solutions of the three common mineral acids produces an unidentified yellow substance, whereas *trans*-azobenzene does not do so even on exposure to sunlight.

Between stilbene and azobenzene there is a measure of stereochemical analogy. In both cases the molecules can achieve a *cis*-configuration only at the expense of the coplanarity of the aromatic rings and the C=C or N=N systems. In particular, the repulsion between the *o*-hydrogen atoms in the *cis*-arrangement of azobenzene requires the two Ar rings to be twisted out of the C–N=N–C plane by 50°. This distortion (evidence for which has come from Robertson's *X*-ray data, *J.*, 1939, 232; *Proc. Roy. Soc.*, 1939, **171**, *A*, 398) is responsible for a reduction in the resonance between the central double bonds and the rings, leading immediately to an explanation for the greater potential energy of the *cis*-isomer compared with the *trans*-. Similar conclusions have been reached from considerations of scale drawings in other chemical problems (cf. Sidgwick, *Ann. Reports*, 1932, **29**, 64; Calderbank and Le Fèvre, *J.*, 1949, 1462).

FIG. 6.

*Benzene-*syn*-diazosulphonate.*



Figs. 6(*a*) and (*b*) represent the *cis*-configuration of the molecule $C_6H_5{\cdot}N{:}N{\cdot}SO_3K$. It has been assumed that (1) the N=N–S system is coplanar with the benzene ring, and that (2) the SO_3 group is tetrahedral (Pauling, " Nature of the Chemical Bond," Cornell, 1942, 240) about the sulphur atom and rotates freely about the N–S axis (the oxygen atoms are shown in the two extreme lateral positions which define the cross-section of the path swept out by the three atoms). The heavy lines represent atomic radii as follows (Pauling and Huggins, *Z. Krist.*, 1934, **87**, 205; Schomaker and Stevenson, *J. Amer. Chem. Soc.*, 1941, **63**, 37): C(aromatic) = 0·70, H = 0·37, N = 0·70, S = 1·04, O = 0·74 A. The broken lines around some atoms denote Stuart's " Wirkungsradien " (*Z. physikal. Chem.*, 1935, *B*, **27**, 350). The nitrogen valency angles have been taken as 125° for the *cis*-form and 121° for the *anti*-form (from azobenzene). The S–O distance has been taken to be 1·50 A., the value for the distance in the sulphate ion; it has thus almost certainly been underestinated (normal S–O distance = 1·70 A.). In the absence of information regarding the method of fixation of the water molecule essential for the existence of the *syn*-isomer, no account has been taken of water of crystallisation in constructing the diagrams. The argument which follows seems reasonable, no matter what the position of the water molecule in the solid compound; certainly, no doubts arise from this direction as far as properties in solution are concerned.

Fig. 6(*a*) provides an explanation for the instability and reactivity of the labile diazosulphonate, assumed as a *syn*-form of the stable *anti*-isomer shown in Fig. 7. It is clear, even without invoking the Wirkungsradien, that steric interference prevents the molecule from assuming the planar structure of Fig. 6(*a*). In Fig. 6(*b*) an end-view of the same molecule [*i.e.*, 6(*a*) seen by looking at it in the plane of the paper from the right edge of the page] has been drawn. The N=N–S system has, however, been turned by 90° about the C–N axis, thus bringing it into a plane perpendicular to the benzene ring. Inspection of this diagram shows the

possibility of the existence of a *syn*-molecule in this state. Measurement of the minimum angle through which the N=N–S plane must be turned from the coplanar condition of Fig. 6(*a*) to avoid the steric hindrance yields a result of 70—50°, according to the extent to which the Stuart radii are considered. This angle of minimum distortion is of the same order as that reported by Robertson *et al.* for *cis*-azobenzene.

It is of interest that no steric factors would enter the discussion, if the labile isomer had the *anti*-diazosulphite structure advocated by Bamberger and Hodgson. Purely for the purpose of comparison, one of the possible configurations of the *syn*-diazosulphite is drawn in Fig. 8 (this formula was first mentioned—and rejected on the same grounds as the *anti*-diazosulphite—by Hantzsch). On the basis of Fig. 8 the *syn*-diazosulphite is not impossible on steric grounds. In the configuration shown, smaller repulsive inter-action is indicated; some of the alternative positions of the SO_2 group, obtained by rotation of the O·SO_2 about the N–O link, would by accompanied by steric interference with the *o*-hydrogen atom.

Finally, because of the other analogies between the diazosulphonates and diazocyanides, the same metrical process has been applied to the *syn*-isomer of benzenediazocyanide (Fig. 9). The diagram shows the likelihood of repulsion between the –C≡N group and the *o*-hydrogen atom, leading to probable non-coplanarity of the benzene ring and the N=N–CN system. The necessary deviation from the coplanar condition seems to be smaller than for the corresponding sulphonate; this observation is compatible with the known decreased instability and velocity of isomerisation of the diazocyanides relatively to the sulphonates.

These speculations also lead to a possible reason for the existence of only one of the two

FIG. 7.

Benzene-anti-*diazosulphonate.*

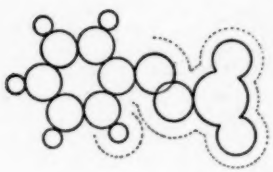


FIG. 8.

Benzene-syn-*diazosulphite.*

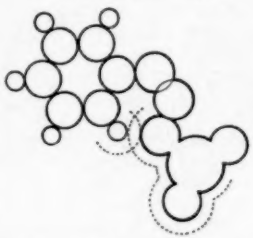
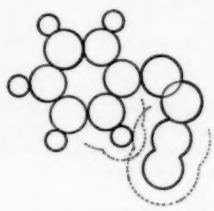


FIG. 9.

Benzene-cis-*diazocyanide.*



predicted isomers of 2 : 4 : 6-tribromobenzenediazosulphonate. This isomer has the stability of the *anti*-diazosulphonates, together with the coupling ability of the *syn*-isomers. It is not impossible—though it requires experimental proof—that the form which is isolated is an unusually stable *syn*-isomer, whose stability is ascribable to the same causes as the generally increased stability of halogenated diazosulphonates, and whose isomerisation by rotation about the N–N bond is prevented sterically (analogously to the hindered racemisation of some 2 : 2′ : 6 : 6′-substituted diphenyls). It is relevant that the isomerisation of 2 : 4 : 6-tribromobenzenediazocyanide has an exceptionally low reaction-rate constant (*J.*, 1949, 944).

It can therefore be concluded by purely theoretical considerations that, if the labile isomers of the diazo-sulphonates and -cyanides exist in *syn*-configurations, then their molecules are non-planar. In such distorted species, the conjugation of the –N=N– bond with the aromatic ring will be reduced, and instability of the *syn*- relatively to the *anti*-isomers is predictable.

EXPERIMENTAL.

Preparation of Diazosulphonates.—In general, the amine (0·1 g.-mol.) was diazotised in 5N-hydrochloric acid (30 ml.) at 0—5° by sodium nitrite (0·1 g.-mol.). The diazo-solution was stirred into an ice-cold solution of sodium sulphite crystals (0·1 g.-mol.) and sodium carbonate (0·35 g.-mol.) in water (150 ml.). The precipitated *syn*-diazosulphonate was filtered off after being washed with three 10-ml. quantities of iced water. With benzidine, it was found necessary to dissolve the amine in the minimum of alcohol before precipitating the hydrochloride from the hot alcoholic solution. The diazotisation then proceeded smoothly.

Some difficulty was experienced in repeating the preparation of potassium 2 : 4 : 6-tribromobenzenediazosulphonate (cf. *Ber.*, 1901, **34**, 3338). Instead of isolating the solid diazonium salt before preparing the diazosulphonate, it was better first to diazotise 2 : 4 : 6-tribromoaniline (0·02 g.-mol.) in 18N-sulphuric acid (25 ml.) by adding a solution of potassium nitrite (0·02 g.-mol.) at 10°, and then to mix the filtered diazo-solution with a cold solution of potassium sulphite (0·02 g.-mol.) and potassium carbonate (0·24 g.-mol.) in water (50 ml.).

In every case, the diazo-solution was treated with a small quantity of urea to remove excess of nitrous acid, and was filtered before addition to the sulphite–carbonate mixture.

The stable diazosulphonates were prepared by warming saturated solutions of the unstable isomers, and were recrystallised from hot water. 2 : 4 : 6-Tribromobenzenediazosulphonate was unchanged by this treatment. Sodium *o*-chlorobenzene-*syn*-diazosulphonate consisted of orange needles, which could be dried on a porous tile and kept in a darkened vacuum desiccator over phosphoric oxide at 0° for 1—2 days (Found, for Na-salt : N, 10·81. After 24 hours : N, 11·00. Calc. for $C_6H_4O_3N_2ClSNa,H_2O$: N, 10·75%). *o*-Chlorobenzene-*anti*-diazosulphonate was obtained in yellow needles (Found : N, 11·5. Calc. for $C_6H_4O_3N_2ClSNa$: N, 11·55%).

Potassium 2 : 4 : 6-tribromobenzenediazosulphonate retained its ability to couple slowly with β-naphthol even after its solution had been boiled (a small amount of brown decomposition product being removed by filtration).

The colours of the five pairs of diazosulphonates prepared for the first time were as follows :

Diazosulphonate.	Unstable form.	Stable form.	Diazosulphonate.	Unstable form.	Stable form.
o-Iodobenzene- ...	Bright orange	Yellow	Diphenyl-2-	Yellow-orange	Yellow
p-Iodobenzene- ...	Brown	Yellow-orange	Diphenyl-4-	Orange	Yellow
Diphenyl-4 : 4-bis-	Bright red	Yellow-orange			

Preparation of o-Chlorobenzenediazosulphonic Acid.—The yellow silver salt was precipitated from a solution of the stable sodium diazosulphonate with silver nitrate; after recrystallisation from hot water, it was treated with the calculated quantity of hydrochloric acid. Filtration of the precipitated silver chloride yielded a yellow solution of the diazosulphonic acid; the solid acid was obtained by slow evaporation of the solution under vacuum. Solutions of this compound decomposed on exposure to strong light.

Experiments on Stability, β-Naphthol Coupling, etc.—The solid sodium or potassium unsubstituted and *p*-nitro-benzenediazosulphonates (*syn*) decomposed within 5—30 minutes of formation. The other *syn*-diazosulphonates could usually be preserved for varying lengths of time on porous tiles, the slow deterioration being evident from a gradual darkening of colour. On some occasions, however, sudden decompositions occurred, with the evolution of heat and fumes, the residue being a dark brown, viscous mass. This type of decomposition was completely unpredictable, but was noted whenever the solid was washed with dehydrating solvents (alcohol–ether) and when mechanical impurities were present. These observations, as also the analyses, are in accord with Hantzsch's statement that the labile isomers decomposed when deprived of their one molecule of water of crystallisation.

For several solid *syn*-compounds (sodium salts), where sudden decomposition did not occur, the relative stabilities were compared by naphthol coupling. The solids, kept on porous tiles in a dark place, were tested occasionally, the formation of a dye with alkaline naphthol being the obvious criterion for the presence of *syn*-isomer. The following were typical periods (in hours), at the end of which the compounds mentioned still showed appreciable naphthol-coupling ability :

o-Chlorobenzene-*syn*-diazosulphonate	48
o- and *p*-Iodobenzene-*syn*-diazosulphonates	72
Diphenyl-4 : 4′-bis-*syn*-diazosulphonate	12
Diphenyl-2- and -4-*syn*-diazosulphonates	6—8

The rates of isomerisation of several sodium diazosulphonates were submitted to a similar qualitative comparison. A 1—2% solution of the *syn*-isomer of each pair was kept at room temperature in a dark place. 1-Ml. portions were removed at 10-minute intervals and mixed with 1 ml. of alkaline 1% β-naphthol solution. When only a faint orange colour was noticed for two consecutive tests, the isomerisation was assumed complete. Typical times for complete isomerisation were :

o-Chlorobenzenediazosulphonate	2·5 hrs. (1% soln.)
o-Iodobenzenediazosulphonate	3 hrs. (1% soln.)
p-Iodobenzenediazosulphonate	0·8 hr. (1% soln.)
Diphenyl-4 : 4′-bisdiazosulphonate	*ca.* 10 mins. (2% soln.)
Diphenyl-2-diazosulphonate	*ca.* 10 mins. (2% soln.)
Diphenyl-4-diazosulphonate	*ca.* 10 mins. (2% soln.)

With sodium *o*-chlorobenzenediazosulphonate, a parallel experiment was conducted, with the solution at 0°. This solution still showed a coupling activity after 3 hours, comparable with its original activity.

Action of Light on Sodium o-Chlorobenzene-anti-diazosulphonate.—(i) *Solution.* A 2% solution in distilled water was prepared from the solid. In each of the following tests, 1 ml. of this solution (A) was ultimately tested with 1 ml. of a solution (B) of 2% β-naphthol and 2% potassium hydroxide in water.

(*a*) Fresh (A) gave an orange colour with (B); the mixture was kept in the dark as standard. (*b*) (A), kept in the dark for 2 hours, gave the same colour with (B) as initially. (*c*) (A), exposed for 30 minutes to sunlight, gave a red colour with (B), the first mixture being used as standard for comparison. (*d*) (A), exposed for 30 minutes to ultra-violet radiation from a quartz mercury-vapour lamp, gave a red colour with (B). (*e*) A mixture of (A) and (B) exposed to sunlight gave a red precipitate within 15 minutes. (*f*) A mixture of (A) and (B) exposed to ultra-violet light gave a red precipitate within 15 minutes. (*g*, *h*) (A), exposed to sunlight or ultra-violet light respectively for 30 minutes, then kept in the dark for some hours, gave the same colour with (B) as unexposed (A). (*i*, *j*) Mixtures of (A) and (B) from (*g* and *h*), exposed to sunlight, gave a red precipitate as in (*e*).

(ii) *Solid.* Six strips of filter-paper were soaked in a fresh 2% solution of *o*-chlorobenzene-*anti*-diazosulphonate, and were dried in the oven at 85°. Each paper in turn was treated by one of the methods shown below, and was then tested by moistening with alkaline 2% β-naphthol solution, (B). (*a*) Freshly-dried paper : no colour with (B). (*b*) Paper kept in the dark for 2 hours : no colour with (B). (*c*) Paper exposed to sunlight for 30 minutes : bright orange colour with (B). (*d*) Paper exposed to ultra-violet light for 30 minutes : bright orange colour with (B). (*e*, *f*) Papers exposed to sunlight and ultra-violet light respectively for 30 minutes : small pieces when tested gave a colour with (B). Papers then kept dark for 12 hours still gave a faint orange colour with (B). After 24 hours, no colour was observed. (*g*, *h*) Pieces of the papers from (*e*) and (*f*), which had not been tested with (B), were re-exposed to sunlight for 30 minutes and then gave a bright colour with (B).

The solution-tests were also carried out with the iodobenzenediazosulphonates, with identical results.

Spectroscopic Examination.—Spectra were recorded by means of a Beckman Photoelectric Quartz Spectrophotometer, Model DU. In all cases, M/5000-solutions were prepared by suitable dilutions of more concentrated initial solutions; so as to minimise errors due to differences in concentration from one solution to another, a single solution was used throughout one complete set of absorption curves.

A solution of freshly precipitated sodium *o*-chlorobenzene-*syn*-diazosulphonate, which had been dried for about 5 minutes by thorough grinding on a porous tile, was prepared in distilled water at 0°. This solution was kept in an ice–salt bath, and the spectrum of the *syn*-isomer was recorded : for each wave-length of observation, the cell was re-filled with fresh solution from the bulk. On completion of the readings, a repetition of some of the early readings showed only an insignificant change. During *ca.* 1·25 hours, however, significant isomerisation had taken place.

After 20 hours at room temperature in the dark, the solution was re-examined, and an absorption curve for the *anti*-diazosulphonate was obtained. This coincided within very small limits with a separate curve obtained from a solution of recrystallised *anti*-isomer.

The absorption curves of the various irradiated solutions were obtained with less rigorous precautions against isomerisation than were used in the case of the *syn*-diazosulphonate. Readings were taken at 100-mμ. intervals, and after every 2 or 3 readings, the bulk of the solution was re-irradiated for 15 seconds before the cell was re-filled. Here again the method was justified by the results, a check at the first wave-lengths recorded revealing small changes at the end of the observations; the absorption curves of irradiated solution were not meant to be recorded in detail, generalities being sufficient to support the theory advanced. The solution used for irradiation was the one obtained by isomerisation of the solution used for the *syn*-absorption curve.

An exploratory experiment was conducted, in which the optical density ($D = \log I_0/I$) at 286 mμ. was plotted against time, for a solution " recovering " after irradiation. Temperature control was not attempted, and the concentrations calculated from the readings did not correspond to those for first-order kinetics. With regard to irradiated solutions, no matter how short the period of illumination—15 seconds was the minimum time used—the solution never returned to its original absorption.

The absorption curves above 400 mμ. were also obtained from solutions examined on a Hardy General Electric Recording Spectrophotometer (at the National Standards Laboratory, C.S.I.R.O., Sydney); the extinctions recorded for *syn*- and *anti*-diazosulphonates and an irradiated solution were higher than those obtained with the Beckman instrument, but were similarly related.

Absorptiometric Examination of Thermal syn- *to* anti-*Change of Sodium o-Chlorobenzene Derivatives.*—A 0·001M-solution of freshly precipitated and tile-dried sodium *o*-chlorobenzene-*syn*-diazosulphonate in distilled water was kept in a thermostat at 20°; the water in the latter was dyed red to prevent stray photochemical effects. Samples were taken at 3—5-minute intervals, and their absorptions measured at once with a Hilger Spekker Photoelectric Absorptiometer, model H454. Water was found to be a suitable reference liquid. The solutions were examined in a 1-cm. cell, a Wood's glass filter and mercury-vapour lamp being used to isolate the 3560·1 A. line. The instrument had previously been calibrated with the *anti*-diazosulphonate, giving, with this salt, a linear plot of concentration against scale-reading for the light used. A similar relation had to be assumed for the *syn*-isomer. The results could not be reconciled with first-order kinetics. The first-order velocity constants (k) calculated are shown below. A check was made to ensure that exposure of the solution to the ultra-violet light of the instrument for the duration of a reading had no effect on the result.

t (mins.)	1	4	7	10	14	17	24·5
k_{20} (mins.$^{-1}$)	0·787	0·822	0·833	0·648	0·528	0·533	0·518
t (mins.)	29	33·5	39	45	62	81	106
k_{20} (mins.$^{-1}$)	0·438	0·398	0·342	0·337	0·297	0·282	0·343

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UNIVERSITY OF SYDNEY, N.S.W., AUSTRALIA. [*Received, August 14th*, 1950.]

93. *Magnetochemistry of the Heaviest Elements. Part III. The Halides of Ter- and Quadri-valent Uranium.*

By J. K. Dawson.

Uranium tetrafluoride, tetrachloride, and tetrabromide obey the Weiss–Curie law over the temperature range 77—550° K. The values obtained for the magnetic moment of the quadrivalent uranium ion indicate that in these compounds the ion has a $5f^1$ electron configuration. Uranium trichloride, tribromide, and tri-iodide deviate from the Weiss–Curie law below about 350° K. and are anti-ferromagnetic; the results are interpreted as arising from a $5f^1.6d^1$ electron configuration for the tribromide and tri-iodide, but the electron assignment is not conclusive for the trichloride.

A study of the magnetic properties of compounds of the elements beyond actinium should provide a useful approach to the elucidation of the most stable electronic states of their respective ions. Results previously reported on quadrivalent uranium compounds are rather scattered and occasionally contradictory. For instance, Hutchinson and Elliott (*J. Chem. Physics*, **1948**, **16**, 920) report the moments of the hydrated sulphate, hydrated oxalate, and the acetylacetone complex as 3·52, 3·75, and 3·39 Bohr magnetons, respectively, the electronic ground state being a $5f^2$ configuration. On the other hand, Lawrence (*J. Amer. Chem. Soc.*, **1934**, **56**, 776) found a moment of 2·95 for the sulphate and 2·97 for the anhydrous chloride. Measurements on the latter compound by Bommer (*Z. anorg. Chem.*, **1941**, **247**, 249) gave a moment of 2·7 Bohr magnetons and were interpreted as being indicative of a $6d^1$ electron configuration. Elliott has reported that uranium tetrafluoride has a moment of 3·30 and that the value is very close to this in a series of double fluorides (*Physical Rev.*, **1949**, **76**, 431). In uranium dioxide U(IV) has an effective moment of 3·20 (Part II, Dawson and Lister, *J.*, 1950, 2181). Few measurements have been reported on U(III) compounds: Lawrence (*loc. cit.*) found that the chloride and the sulphate had moments of 3·22 and 3·17 magnetons, respectively. In order to obtain a more complete set of data, the author has investigated the susceptibility–temperature relations of UF_4, UCl_4, UBr_4 and of UCl_3, UBr_3, and UI_3.

Experimental.

The measurements were made on the balance described in Part I (*J.*, 1950, 2177), the samples being enclosed in sealed capillary tubes under an atmosphere of dry nitrogen. The order of measurements on each sample was: room temperature, low temperatures, high temperatures, room temperature; by this means a check was made against decomposition of the sample at high temperatures. A second sample from a separate preparation was taken over the same range of temperatures and good agreement

Uranium tetrafluoride.

T, °K.	$10^6\chi$, g.	$10^6\chi$ per U(IV).
77	21·82	6912
90	20·62	6536
198	13·20	4206
295	10·10	3232
334·5	9·04	2900
416	7·80	2510
500	6·72	2171

Uranium tetrachloride.

T, °K.	$10^6\chi$, g.	$10^6\chi$ per U(IV).
90	23·41	8919
196	13·30	5177
294	9·68	3802
333	8·64	3406
372	7·87	3114
388	7·56	2996
413	7·09	2818
441	6·74	2684
551	5·89	2363

Uranium tetrabromide.

T, °K.	$10^6\chi$, g.	$10^6\chi$ per U(IV).
77	19·27	10,930
90	17·30	9,828
197	9·15	5,281
293	6·33	3,709
359	5·21	3,083
383·5	4·87	2,894
418·5	4·49	2,680
455	4·15	2,491
513	3·68	2,229
569	3·32	2,032

Uranium trichloride.

T, °K.	$10^6\chi$, g.	$10^6\chi$ per U(III).
90	25·97	8952
198	14·78	5095
300	10·03	3456
367	8·41	2899
395	7·86	2709
426	7·34	2530
456	6·88	2372
490	6·35	2189
509	6·18	2130

Uranium tribromide.

T, °K.	$10^6\chi$, g.	$10^6\chi$ per U(III).
90	23·95	11,600
198	14·32	7,005
294	9·91	4,896
342	8·54	4,243
368	7·91	3,942
394	7·38	3,687
439	6·48	3,256
457	6·19	3,119
483	5·83	3,949

Uranium tri-iodide.

T, °K.	$10^6\chi$, g.	$10^6\chi$ per U(III).
77	21·50	13,520
90	19·59	12,340
197	10·60	6,779
293	7·20	4,673
337	6·29	4,111
352	6·02	3,943
365	5·76	3,784
394	5·32	3,509

was obtained in each case. Reproducible results on the tri-iodide were found to be possible only on freshly prepared material, and no agreement was obtained between several samples of the tetraiodide, which is therefore omitted from this discussion.

The UCl_3, UI_3, and UBr_4 were prepared directly from samples of the same batch of uranium metal turnings in a graded furnace according to the methods of Gregory (Manhattan District Declassified Document, 1755). A spectrographic analysis of the UI_3 gave <0·01% by weight of iron, chromium, nickel, cobalt, and manganese combined. Uranium tribromide was formed by hydrogen-reduction of the tetrabromide. Uranium tetrachloride was prepared by reaction of the iron-free oxide with carbon tetrachloride, followed by sublimation of the product *in vacuo*. The tetrafluoride was a good commercial grade.

The results are given in the table, the figures in the third column for each compound being obtained after correction for the diamagnetism of the anions and the cations. These values were calculated by Angus's method (*Proc. Roy. Soc.*, 1932, *A*, **136**, 569) and were $F^- = -7{\cdot}25 \times 10^{-6}$, $Cl^- = -22{\cdot}9 \times 10^{-6}$, $Br^- = -36{\cdot}65 \times 10^{-6}$, $I^- = -55{\cdot}3 \times 10^{-6}$, U(IV) $= -31{\cdot}5 \times 10^{-6}$, U(III) $= -53{\cdot}3 \times 10^{-6}$. The values for the uranium ions are calculated by using an electron configuration of $5f^2$ for U(IV) and $5f^2 \cdot 6d^1$ for U(III).

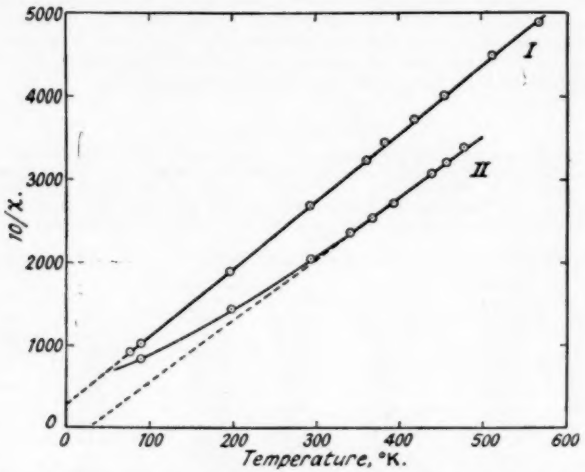
Discussion.

The Weiss constants and the magnetic moments calculated by the Weiss–Curie law from the data in the above table are given below. The tetrahalides follow the Weiss–Curie law over the temperature range studied, but the trihalides show marked deviations at lower tem-

Compound.	UF_4.	UCl_4.	UBr_4.	UCl_3.	UBr_3.	UI_3.
Δ	−116°	−62°	−35°	−29°	+25°	+5°
μ per U ion	3·28	3·29	3·12	3·03	3·29	3·31

peratures and the moments quoted are those obtained in the higher temperature region. The susceptibility–temperature behaviour of the two groups of compounds is compared in the figure.

In the case of the tetrahalides the variation of Δ from fluoride to bromide is such as may be



I. Reciprocal susceptibility–temperature curve for the U(IV) *ion in* UBr_4.
II. Reciprocal susceptibility–temperature curve for the U(III) *ion in* UBr_3.

expected from the trend of molar volumes, and most of the change in Δ would seem to arise from Heisenberg exchange interaction rather than variation in the crystalline field splitting. The measured magnetic moments for U(IV) can be explained on the assumption of a $5f^2$ electron configuration with the exchange effect and the crystalline field splitting reducing the effective moment below the theoretical value of 3·58 Bohr magnetons for Russell–Saunders coupling. The calculated value for j–j coupling is 3·83, and the same conclusions would still apply.

Although there is a greater amount of covalent nature in the tetrabromide than in the

tetrafluoride, in view of the comparative constancy of the effective moment the orbitals concerned do not seem to involve 5*f* hybrids.

The situation is rather different for the tervalent compounds, however. The appearance of a positive Δ value in the bromide and iodide, together with deviations from the Weiss–Curie law, indicate that the electron additional to those in the U(IV) ion is of a different species. The situation is comparable with that in the transition elements (*e.g.*, Klemm and Grimm, *Z. anorg. Chem.*, 1942, **249**, 209) and is indicative of the strong parallel coupling of adjacent spin vectors to be expected for unshielded outer electrons. The trichloride shows a less intense coupling, but still deviates from the Weiss–Curie law at low temperatures. The " spin-only " value of the effective moment for three electrons is 3·87 Bohr magnetons. The lowest-lying energy levels predicted by Hund's rule for Russell–Saunders coupling are $4I_{9/2}$ ($\mu_{eff.} = 3{\cdot}62$) and $4K_{11/2}$ ($\mu_{eff.} = 4{\cdot}60$) for $5f^3$ and $5f^2 . 6d^1$ configurations, respectively; *j*–*j* coupling gives effective moments a little higher than the L–S coupling, and a further low-lying state for the $5f^2 . 6d^1$ configuration is $4H_{7/2}$ ($\mu_{eff.} = 2{\cdot}65$), corresponding to complete orbital quenching of the 6*d* electron. In view of the various types of coupling and quenching theoretically possible in this case, it is difficult to deduce an unambiguous electron configuration by comparison of the observed and calculated moments, but the observed value of about 3·3 magnetons is not inconsistent with a $5f^2 . 6d^1$ configuration in which the orbital contribution of the 6*d* electron is quenched together with partial quenching of the 5*f* electrons, and in which there is strong spin coupling between adjacent 6*d* electrons. This spin coupling would not have been expected by comparison with the $5f^2$ configuration of the U(IV) ion and does not occur in the corresponding rare-earth ion. Consequently, the magnetic data are interpreted as arising from electrons in a $5f^2.6d^1$ configuration in the tribromide and tri-iodide. The coupling is not so great in the trichloride and it is not possible on these results definitely to assign the third electron to either the 5*f* or the 6*d* level.

A preliminary experiment on the effect of dilution of uranium tribromide with isomorphous lanthanum bromide shows that at 90% dilution the susceptibility of the U(III) ion follows the Weiss–Curie law much more closely and the moment rises higher than 4·6 magnetons, but there remains a rather high Δ value which presumably arises from the crystalline field effect.

The author acknowledges assistance in various phases of this work from several members of this Establishment: in particular, useful discussions with Mr. C. J. Mandleberg and the preparation of a number of samples by Mr. A. Truswell. The paper is published by permission of the Director, A.E.R.E., Harwell.

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94. β-*Aroylpropionic Acids. Part II. The Action of* o- *and* p-*Methoxyphenylmagnesium Bromide on Succinic Anhydride.*

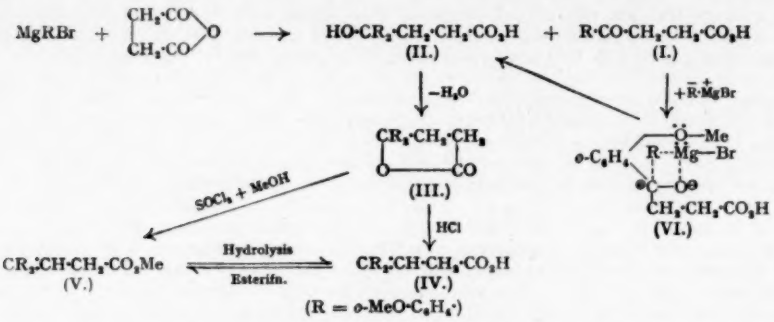
By F. G. Baddar and Lanson S. El-Assal.

o-Methoxyphenylmagnesium bromide and succinic anhydride give a mixture of β-*o*-methoxybenzoylpropionic acid and γ-hydroxy-γγ-di-*o*-methoxyphenylbutyric acid; the latter acid is converted into its lactone when refluxed with alcohol. The lactone gives, when refluxed with concentrated hydrochloric acid, 3 : 3-di-*o*-methoxyphenylprop-2-ene-1-carboxylic acid (IV) which on oxidation with potassium permanganate gives 2 : 2′-dimethoxybenzophenone. When the lactone is treated with thionyl chloride followed by methyl alcohol, it gives the methyl ester of the acid (IV).

p-Methoxyphenylmagnesium bromide and succinic anhydride give mainly β-*p*-methoxybenzoylpropionic acid.

In an attempt to prepare β-*o*-methoxybenzoylpropionic acid by the action of *o*-methoxyphenylmagnesium bromide on succinic anhydride (cf. Hill *et al.*, *J.*, 1937, 1621; Lockett and Short, *J.*, 1939, 789), a product was obtained, which was proved to be a mixture of β-*o*-methoxy-

benzoylpropionic acid (I) and chiefly γ-hydroxy-γγ-di-*o*-methoxyphenylbutyric acid (II) (cf. Weizmann, E. Bergmann, and F. Bergmann, *J.*, 1935, 1367; Weizmann, Blum-Bergmann, and F. Bergmann, *ibid.*, p. 1370). The acid (II) was converted into its lactone (III) when refluxed



with alcohol. The structure of (III) was elucidated from the following facts: (i) It was identical with the product obtained by the action of *o*-methoxyphenylmagnesium bromide on β-*o*-methoxybenzoylpropionic acid. (ii) When the lactone was refluxed with concentrated hydrochloric acid for an hour, it was converted into 3 : 3-di-*o*-methoxyphenylprop-2-ene-1-carboxylic acid (IV), which was oxidised by cold alkaline potassium permangante to 2 : 2′-dimethoxybenzophenone. Esterification of the lactone (III) with thionyl chloride and methyl alcohol gave the methyl ester of the acid (IV).

The formation of the propene acid (IV) from the lactone (III) by boiling hydrochloric acid is similar to the isomerisation of γ-phenylbutyrolactone to 3-phenylprop-2-ene-1-carboxylic acid (cf. Fittig and Hadorff, *Annalen*, 1904, **334**, 119). Similarly, the formation of the unsaturated ester (V) from the lactone (III) by the action of thionyl chloride and methyl alcohol could be explained by assuming first the formation of the acid chloride of (IV), which readily reacts with methyl alcohol to give the unsaturated ester (V).

However, when *p*-methoxyphenylmagnesium bromide was similarly treated with succinic anhydride, it gave β-*p*-methoxybenzoylpropionic acid as the main product. Similarly, when the latter acid was treated with *p*-methoxyphenylmagnesium bromide, it was mainly recovered unchanged. The abnormal reactivity of the *o*-methoxy-acid compared with the *p*-methoxy-acid may be due to the co-ordination of a molecule of the Grignard reagent with the ethereal oxygen atom of the methoxyl group in (I), leading to a complex in a transition state (VI) which gives rise to the acid (II). The formation of such a transition state is impossible with β-*p*-methoxybenzoylpropionic acid. The validity of this assumption is under investigation.

Experimental.

[M. p.s are uncorrected. Microanalyses were carried out by Drs. Weiler and Strauss, Oxford.]

γγ-Di-o-methoxyphenylbutyrolactone (III).—(i) An ethereal solution of *o*-methoxyphenylmagnesium bromide [from freshly distilled *o*-bromoanisole (24·0 g., 1 mol.) and magnesium (3·1 g., 1 mol.) in dry ether (80 c.c.)] was added dropwise to a boiling solution of succinic anhydride (12·5 g., 1 mol.) in dry, thiophen-free benzene (200 c.c.), and the whole boiled under reflux for 2·5—3 hours, and left overnight at room temperature. The product was worked up as usual, and the benzene–ether layer was extracted with sodium hydroxide solution (charcoal). The acid precipitated on acidification (10 g.) was refluxed with absolute alcohol for 1—1·5 hours, the alcohol evaporated, and the residue extracted with cold sodium carbonate solution. The insoluble product was filtered off (*ca.* 5 g.), and crystallised from alcohol to give the *lactone* in colourless shining crystals, m. p. 177—178° [Found: C, 72·4; H, 6·0; OMe, 21·1%; *M* (Rast), 288. $C_{18}H_{18}O_4$ requires C, 72·5; H, 6·0; OMe, 20·8%; *M*, 298].

The sodium carbonate solution gave on acidification an acid (*ca.* 3 g.) which, when crystallised from benzene–light petroleum (b. p. 40—60°), gave β-*o*-methoxybenzoylpropionic acid (I) in colourless crystals, m. p. 100—101°, undepressed on admixture with an authentic specimen (see Part I; *J.*, 1950, 3606) (Found: C, 63·6; H, 5·5; OMe, 16·3%; *M*, 198. Calc. for $C_{11}H_{12}O_4$: C, 63·5; H, 5·8; OMe, 14·9%; *M*, 208). Dauben and Tanabe (*J. Amer. Chem. Soc.*, 1949, **71**, 2878) and Dauben and Tiller *J. Org. Chem.*, 1950, **15**, 788) give m.p. 95·6—96·6° and 93·5—95°, respectively.

The lactone was insoluble in cold 20% sodium hydroxide solution, and dissolved with difficulty on refluxing for 2—2·5 hours. It resisted the action of hot alkaline potassium permanganate solution.

(ii) *o*-Methoxyphenylmagnesium bromide [from *o*-bromoanisole (4·1 g., 2·1 mols.), magnesium (0·54 g., 2·2 mols.), ether (50 c.c.)] was added dropwise during 20 minutes to a boiling solution of β-*o*-methoxybenzoylpropionic acid (2·1 g., 1 mol.) in dry, thiophen-free benzene (50 c.c.), and worked up as above. The product insoluble in sodium carbonate solution was filtered off (*ca.* 1 g.), and crystallised from alcohol to give the same lactone as in (i), m. p. and mixed m. p. 177—178° (Found: C, 72·1; H, 6·2; OMe, 20·3%; *M*, 310).

3 : 3-*Di*-o-*methoxyphenylprop*-2-*ene*-1-*carboxylic Acid* (IV).—The lactone (III) (1 g.) was refluxed with concentrated hydrochloric acid (20 c.c.) for 1 hour. The product was extracted with sodium carbonate solution, and the extract gave on acidification a crystalline precipitate. On crystallisation from benzene–light petroleum (b. p. 40—60°), the *acid* (IV) was obtained in colourless crystalline aggregates (*ca.* 0·8 g.), m. p. 134—135° (Found: C, 72·2; H, 6·0; OMe, 20·5%; *M*, 280. $C_{19}H_{18}O_4$ requires C, 72·5; H, 6·0; OMe, 20·8%; *M*, 298). The alkaline solution of this acid discharged the colour of potassium permanganate solution.

Methyl ester (V). (i) The above acid was esterified by use of thionyl chloride and methyl alcohol. The product, crystallised from light petroleum (b. p. 40—60°), gave the *methyl* ester, m. p. 64—65° (Found: C, 72·7; H, 6·2; OMe, 30·6%; *M*, 327. $C_{19}H_{20}O_4$ requires C, 73·1; H, 6·4; OMe, 29·8%; *M*, 312), which, on hydrolysis with alcoholic potassium hydroxide solution, regenerated the original acid.

(ii) A solution of the lactone (3 g.) in benzene (10 c.c.) was refluxed for 30 minutes with thionyl chloride (3 c.c.). The benzene and excess of thionyl chloride were distilled off, and the residue refluxed with methyl alcohol for 2 hours. The alcohol was evaporated, and the product extracted with ether, washed with dilute sodium carbonate solution, and dried (Na_2SO_4). Removal of the ether left a residue which crystallised from light petroleum (b. p. 40—60°) to give the same methyl ester (2·4 g.) as was obtained in (i); m. p. and mixed m. p. 64—65° (Found C, 73·1; H, 6·2; OMe, 29·6%; *M*, 307).

Oxidation of the Acid (IV).—Potassium permanganate (1·8 g., 4 mols.) was added portionwise at room temperature (20—30°) to a solution of 3 : 3-di-o-methoxyphenylprop-2-ene-1-carboxylic acid (0·5 g., 1 mol.) in potassium carbonate solution, and the mixture left for 3—4 days with occasional shaking. Excess of permanganate was destroyed with hydrogen peroxide, and the precipitated manganese dioxide was filtered off and dried. Both the precipitate and the mother-liquor were thoroughly extracted with ether, and the ethereal solution was washed with dilute sodium hydroxide solution and dried. The product from the ether crystallised from methyl alcohol to give colourless crystals of 2 : 2′-dimethoxybenzophenone, m. p. and mixed m. p. 104—105° [Found: C, 74·4; H, 5·6; OMe, 24·1%; *M* (Rast), 224. Calc. for $C_{15}H_{14}O_3$: C, 74·4; H, 5·8; OMe, 25·6%; *M*, 242]. If the product failed to crystallise, it was purified by vacuum distillation. 2 : 2′-Dimethoxybenzophenone, prepared for comparison by methylation of 2 : 2′-dihydroxybenzophenone (see Graebe and Feer, *Ber.*, 1886, **19**, 2609) with methyl iodide and anhydrous potassium carbonate in dry acetone (see methylation of β-*o*-hydroxybenzoylpropionic acid, Part I, *J.*, 1950, 3606), crystallised from methyl alcohol in colourless crystals, m. p. 104—105° (Found: C, 74·3; H, 5·6; OMe, 25·6%; *M*, 222).

Action of p-*Methoxyphenylmagnesium Bromide on Succinic Anhydride*.—By essentially the same procedure as for the *o*-compound, this Grignard reagent (from *p*-bromoanisole, 8·8 g., 1 mol.) was caused to react with succinic anhydride (4·7 g., 1·1 mols.), and the mixture was worked up as above, yielding ultimately β-*p*-methoxybenzoylpropionic acid (*ca.* 4 g.), m. p. and mixed m. p. 151—152° (Found: C, 63·5; H, 5·9; OMe, 14·2%; *M*, 215).

Action of p-*Methoxyphenylmagnesium Bromide on* β-p-*Methoxybenzoylpropionic Acid*.—The bromide [from *p*-bromoanisole (9·5 g., 2·1 mols.), magnesium (1·3 g., 2·2 mols.), ether (60 c.c.)] was added dropwise during 20 minutes to a boiling solution of β-*p*-methoxybenzoylpropionic acid (4·6 g., 1 mol.) in dry, thiophen-free benzene (100 c.c.), and worked up as above. The acid product (*ca.* 3·2 g.) was unchanged β-*p*-methoxybenzoylpropionic acid (m. p. and mixed m. p.). The remaining ether–benzene solution was evaporated to dryness and the viscous oily residue was cooled and extracted with cold alcohol. The residual solid (*ca.* 1·2 g.), well washed with alcohol, had m. p. 196—197°. This crystallised from benzene–light petroleum (b. p. 40—60°) in lemon-yellow crystals, m. p. 198—199°; it was recovered unchanged when refluxed for 3 hours with concentrated hydrochloric acid or 20% sodium hydroxide solution, showing that it could not be a lactone; also it was not 4 : 4′-dimethoxydiphenyl. Its constitution is under investigation.

FOUAD I UNIVERSITY, FACULTY OF SCIENCE, CAIRO, EGYPT. [*Received, September 22nd*, 1950.]

95. *Comparison of Weak Neutron Fluxes by Use of Organic Bromides.*

By P. F. D. Shaw and C. H. Collie.

A quantitative study has been made of some of the factors influencing the reproducibility of extractions (using an aqueous extracting agent) of radio-bromine from neutron-irradiated ethyl bromide, bromobenzene, and ethylene dibromide with a view to furnishing a sensitive method of comparing weak neutron fluxes. The chief cause of non-reproducibility of extractions of these substances is the presence of olefinic impurities produced by the recoiling radio-bromine atoms. Evidence for the stability of the methylene molecule has been obtained. By irradiating specimens containing a trace of elementary bromine, and by making corrections when necessary for exchange between the extractable radioactive species and the bulk of the (inactive) liquid, extractions can be made reproducible to better than $\pm 1\%$.

Aniline present during the neutron-irradiation of ethylene dibromide reduces the amount of radio-bromine extractable with potassium bromide, owing to the formation of bromoaniline, but at the same time reduces the exchange occurring in the pure liquid, and if present in sufficient quantity, increases the amount of extractable radio-bromine by playing a direct part in the γ-recoil process (cf. Lu and Sugden, *J.*, 1938, 1273).

The work described in this paper is an extension of a method of comparing weak neutron fluxes reported previously (Shaw and Collie, *J.*, 1949, 1217). The latter made use of the Szilard–Chalmers effect (*Nature*, 1934, **134**, 462) in ethyl iodide, by means of which about half of the radio-iodine produced by the reaction ^{127}I (n, γ) ^{128}I can be extracted with an aqueous reagent and concentrated so that the reduction in activity caused by self-absorption effects is small. The method suffers from a defect that in certain physical applications (*e.g.*, see Halban, Kowarski, and Magat, *Compt. rend.*, 1939, **208**, 572) the time elapsing between the removal of the neutron source and the measurement of the extracted radio-halogen is necessarily large compared with 25 minutes (the half life of ^{128}I), and consequently there is a serious loss of measurable activity. This difficulty can be reduced by using organic bromides as the detectors, since some of the bromine isotopes [^{80}Br (excited state) and ^{83}Br] produced by neutron capture have longer half-lives (4·4 and 34 hours respectively).

The compounds investigated were ethyl bromide, bromobenzene, and ethylene dibromide. It was found that in the presence of small quantities of elementary bromine the reproducibility of extraction of radio-bromine from the neutron-irradiated halides could be made better than 1%. In the absence of bromine none of these compounds purified by conventional methods could be made to give reproducible extractions; the extent of this irreproducibility is indicated in Table I which gives the efficiency of extraction (the activity extracted/total activity produced $\times$ 100 = 100 − the " retention ") for these substances under different conditions.

Table I.

Compound.	Efficiency of extraction. Pure compound.	(All compounds irradiated to saturation at 15°.) Compound + 0·01 g. of Br_2/100 c.c.
Ethyl bromide	35 ± 10 *†	54 ± 3 †
Ethylene dibromide	45 ± 10 *†	62 ± 2
Bromobenzene	27 ± 10 *	55 ± 2

* Not reproducible. † " Exchange " occurs.

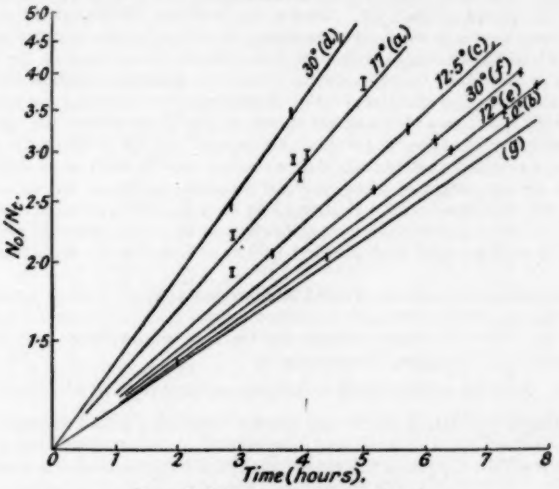
The object of this paper is to give an account of the stabilising action of traces of elementary bromine in extractions of the above organic bromides and to discuss the optimum conditions for their use as neutron detectors.

In this paper, the term " exchange " is used extremely loosely to describe the slow disappearance of the extractable radioactive species by any means other than decay; as will be seen later, although sometimes this may refer to a true chemical exchange between the extractable radio-bromine and the bulk of the (inactive) organic bromide, under certain conditions the extractable radio-bromine probably disappears by some other mechanism.

Ethyl Bromide.—In the absence of elementary bromine, a considerable, variable fraction (up to 40%) of the extractable radio-bromine adhered to the walls of the irradiation flask.

The adsorbed material was easily removed by washing with potassium bromide solution and was incorporated with the main aqueous extract. Thus while loss caused by variable adsorption was not in itself a cause of variation it was thought possible that it might indirectly be the cause of the variable results obtained under these conditions. If the rate of exchange between the extractable radio-bromine and the bulk of the ethyl bromide was different when the former was adsorbed or in the liquid, the overall exchange rate would be variable and would lead to variation in the activity extracted. The exchange was followed by splitting irradiated specimens of ethyl bromide into two aliquots, extracting one immediately and leaving the other for a variable time before extraction. The exchange curve obtained is shown in Fig. 1, curve (*a*); the variation in the exchange rates was not sufficient to account for the variation in the activity extracted initially, which varied from 9400 to 15800 counts/10 minutes. No marked correlation was observed between the amount of extractable radio-bromine adhering to the walls and the

FIG. 1.



N_t = *Activity extractable after time t.*

|, *Purified* C_2H_5Br; +, $C_2H_5Br + Br$; I (*curve a*), *see text*; *g*, *Natural radioactive decay.*

magnitude of the activity extracted initially. A more probable explanation of the variation in the rate of exchange is that the exchange proceeds by the mechanism :

$$HBr^* + C_2H_5Br \rightleftharpoons HBr + C_2H_5Br^*$$

and that the concentration of hydrogen radio-bromide present is dependent on the exchange :

$$HBr^* + Br_2 \rightleftharpoons HBr + Br - Br^*$$ (cf. Topley and Weiss, *J.*, 1936, 912)

i.e., is dependent on the concentration of elementary radio-bromine present. Reasons for supposing that the latter quantity (and hence the exchange) is not constant are given later.

In all experiments the isotope whose disintegration was measured was the excited state of ^{80}Br (4·4 hours, half-life), and hence measurements were unaffected by the possibility of extra activity accruing in the extractable fraction owing to the formation of 18-minutes ^{80}Br produced by the radioactive decay of the excited state (cf. Segré, Halford, and Seaborg, *Physical Rev.*, 1939, **55**, 321).

If a large quantity of ethyl bromide was purified (as described later), portions of this gave extractions consistent (to within $\pm 2\%$) with those from other irradiated portions of the same batch, provided that an aliquot used for an irradiation and extraction was not re-mixed with it. On repetition of the purification process reproducible results were again obtained with specimens from the purified batch, although the activities obtained under identical irradiation (etc.) conditions were different from those of the first batch. By using quantities from such purified batches it was possible to construct exchange curves by the method described for ethyl iodide (Shaw and Collie, *loc. cit.*); the results obtained are shown in Fig. 1, curves (*b*), (*c*), and (*d*).

If it is assumed that the back-reaction of the exchange is negligible owing to the fact that effectively all the bromine atoms in the ethyl bromide are inactive, the rate of disappearance of the extractable species may be written $dN/dt = -(\lambda + k)N$, where N is the number of extractable radio-bromine atoms, and λ and k are the radioactive decay and exchange constants respectively. By integration, this becomes $\ln (N_0/N_t) = (\lambda + k)t$, where N_0 and N_t are the number of extractable radio-bromine atoms present at times = 0 and t respectively; by subtracting λ from the slopes of the curves shown, the values of k (the fraction exchanging per hour) may be obtained. By equating $k = \alpha \exp(-E/RT)$ where α is a constant and E is the heat of activation for the exchange, one obtains $\alpha = 2{\cdot}4 \pm 0{\cdot}4 \times 10^{15}$ and $E = 21{\cdot}5 \pm 3{\cdot}0$ kcals. per g.-mol. These values are only approximate, owing to the difficulty in obtaining reproducible extractions from batch to batch of ethyl bromide. The value of α is consistent with the view that the exchange occurring is between hydrogen radio-bromide and (inactive) ethyl bromide. The heats of activation between *n*-butyl and *n*-propyl bromides and hydrogen radio-bromide have been measured by Leroux and Sugden (*J.*, 1939, 1279) and Elliot and Sugden (*J.*, 1939, 1836) in ionising solvents and found to be 18·87 and 18·13 kcals./g.-mol. respectively; the nearness of these figures to the activation energy found might also add corroborative evidence for the mechanism of the exchange, although it is difficult to conceive of an ionic mechanism for the exchange in pure ethyl bromide, owing to the low dielectric constant of this substance.

In the presence of small quantities (0·01 g./l.) of elementary bromine the exchange is greatly reduced; the exchange curves obtained are shown in Fig. 1, curves (*e*) and (*f*). The values of α and E (in the same units as above) for this "exchange" are $7{\cdot}6 \times 10^9$ and 9 ± 3 respectively. The low value of α suggests that the reaction occurring may be with some impurity; however, after irradiation to saturation of bromine-ethyl bromide solutions, the activities {which are proportional to the effective half-life τ', defined as $\ln [2/(\lambda + k)]$} obtained were independent, within $\pm$ 1·5%, of the methods used for purification of the ethyl bromide and bromine. The whole anomaly is analogous to that in ethyl iodide, and so far no explanation of it can be advanced.

The reproducibility of extractions of ethyl bromide containing a trace of bromine is illustrated in Table II(*a*); the activities shown are corrected for the radioactive decay occurring between extraction (at the time of removal from the neutron source) and measurement, and to "saturation-irradiation" by using the expression:

$$\text{Activity at saturation} = \text{Activity extracted}/(1 - 2^{-T/\tau'})$$

where T is the time of irradiation and τ' the effective half-life (defined above). As can be seen from Table II(*a*) the activity extracted was independent of the concentration of bromine in the irradiated mixture within the limits indicated; a similar independence has already been shown for ethyl iodide.

The rôle of added iodine in ethyl iodide has been shown to be solely to inhibit the exchange occurring; in ethyl bromide, the bromine appears to do more than this, since if the amount of extractable radio-bromine which would have been obtained had no exchange occurred is calculated by multiplying the activities at saturation by $\tau_{\text{radioactive}}/\tau_{\text{effective}}$, the resulting activity is not the same for ethyl bromide irradiated with and without bromine. It was thought that the variations in the activities extracted from pure ethyl bromide might be ascribed to small ethylenic impurities either present initially owing to incomplete "saturation" of the compound by the purification process or produced by the γ-recoil process. In either case any elementary radio-bromine produced might be expected to add to the double bonds and be lost from the extractable fraction; such an effect would probably be less marked in the case of ethyl iodide, owing to the reluctance of iodine to add to double bonds. The stabilising influence of bromine in ethyl bromide irradiations could then be explained by assuming that the olefinic impurities would be saturated preferentially by the (inactive) bromine present, thus preserving radio-bromine present for extraction. On this basis the variation in the activities extracted from pure ethyl bromide could be ascribed to variable ethylene (etc.) or hydrogen bromide content; in the latter case the amount of elementary radio-bromine present would also be variable owing to exchange of the type:

$$HBr + Br{-}Br^* \rightleftharpoons HBr^* + Br_2$$

which occurs readily even in non-ionising solvents (Topley and Weiss, *loc. cit.*).

The feasibility of this type of explanation was tested by measuring the activity extractable from an aliquot of a purified batch of ethyl bromide [Table II(*b*)], and then repeating the experiment after a little ethylene had been passed into it; the activity obtained is shown in

Table II(*c*), and was significantly less than that shown in (*b*). Attempts were made to confirm the validity of this explanation by adding various carriers to extracted specimens of ethyl bromide and separating them by fractional distillation, a technique used first by Glueckauf and Fay (*J.*, 1936, 390). The activities obtained, expressed as percentages of the total radio-bromine produced are given in Table III; the activities from (*a*) (bromine present during irradiation) are the mean of two experiments. The errors given are statistical only, and in general should be increased by about 3% to cover errors inherent in the method used (see later).

TABLE II.

(*a*) Br (mg./l.).	Activity extracted (per 5 mins.).	(*b*) Activity (per 5 mins.) from purified batch of ethyl bromide.
22	21,600 ± 200	14,900 ± 150
40	21,600 ± 200	14,700 ± 150
45	21,500 ± 200	
55	21,800 ± 200	(*c*) Activity (per 5 mins.) from ethyl bromide used in (*b*) + trace of ethylene.
122	21,900 ± 200	10,300 ± 120
		10,500 ± 120

TABLE III.

Fraction.	0·01 g. of Br per 100 c.c. of C_2H_5Br.	No Br present.		
	(*a*).	(*b*).	(*c*).	(*d*).
(1) CH_2Br	4·02 ± 0·26	4·21 ± 0·23	4·60 ± 0·32	4·65 ± 0·35
(2) CH_2Br_2	4·05 ± 0·20	10·30 ± 0·49	6·12 ± 0·24	9·40 ± 0·42
(3) C_2H_5Br	23·52 ± 1·62	31·41 ± 2·05	34·62 ± 1·94	29·22 ± 1·93
(4) CH_2·$CHBr_2$	3·42 ± 0·24	8·09 ± 0·41	6·95 ± 0·37	7·85 ± 0·36
(5) CH_2Br·CH_2Br	4·53 ± 0·30	13·72 ± 0·61	7·04 ± 0·36	8·31 ± 0·41
(6) CH_2Br·$CHBr_2$	1·92 ± 0·32	6·81 ± 0·35	3·62 ± 0·20	2·29 ± 0·27
(7) $CHBr_2$·$CHBr_2$	1·07 ± 0·12		2·80 ± 0·18	1·93 ± 0·13
Sum of (1) to (7)	42·53 ± 1·76	74·54 ± 2·28	65·75 ± 2·05	63·65 ± 2·11
Sum of (1) to (7) (determined directly)	44·98 ± 2·85	76·10 ± 3·92	68·45 ± 3·74	66·51 ± 4·02
Percentage extracted ...	54·65 ± 2·92	24·95 ± 2·19	31·41 ± 2·20	36·25 ± 2·72

If one assumes (after Libby, *J. Amer. Chem. Soc.*, 1940, **62**, 1930) that the main process responsible for the " slowing-down " of the energetic atoms is collision with other bromine atoms, then about eight collisions are necessary to reduce the translational energy from about 175 ev. to about 1 ev., it being further assumed that on average half the energy is lost per collision. This corresponds roughly to a path length of 20 A. (calculated by using van der Waals radii taken from Pauling, " Nature of the Chemical Bond," 2nd edition, 1945), and, if all the molecules " touched " by the recoiling atom and other bromine atoms (energised by collision) are considered as potentially capable of playing a direct part in the recoil process, the total number of such molecules will be about 30 per recoil. Since the concentration of bromine molecules in run (*a*) (Table III) was 1 per 20,000 ethyl bromide molecules, it appears that the probability of the added bromine playing a direct (or immediate) part in the recoil process was only about 1 per 660 recoils. At higher concentrations of bromine (1—6%) the added bromine may play a significant part in the recoil processes, and evidence for this has been obtained by Lu and Sugden (*loc. cit.*) and Friedman and Libby (*J. Chem. Physics*, 1949, **17**, 647).

It seems probable, therefore, that the activity of the fractions in (*b*), (*c*), and (*d*) in excess of those in (*a*) cannot be explained by direct participation of the bromine present in the recoil processes, but must be caused by slower secondary processes occurring after the recoil. It can be seen that the variation in activity of fractions 5, 6, and 7 can all be explained by assuming that radio-bromine adds to olefinic compounds (acetylene, vinyl bromide, and 1 : 2-dibromo-ethylene, respectively), presumably produced in the recoil process. For example, ethylene may be produced by the disproportionation of two ethyl radicals:

$$C_2H_5\cdot + C_2H_5\cdot \longrightarrow C_2H_6 + C_2H_4$$

(Bawn and Whitby, Faraday Soc. Discussion, " The Labile Molecule," 1947, p. 228). The formation of vinyl bromide may occur by a similar process; the production of dibromoethylene is more difficult to explain but this may be brought about by recombination of highly fragmented ethyl bromide molecules. An alternative explanation is that fraction 7 may contain active heavier molecules (having more than two carbon atoms) for which no carriers were added.

The formation of ethylidene dibromide in variable amount is assumed to be caused by addition of hydrogen radio-bromide to vinyl bromide, although this explanation is open to the objection that hydrogen bromide adds to double bonds extremely slowly under optimum conditions.

The most interesting feature of Table III is the variation in activity of the methylene dibromide fraction. As already indicated, one must seek a relatively slow mechanism for the formation of the methylene radio-bromide produced in the absence of elementary bromine in order to account for the " protective " action of the latter. A feasible explanation to account for this is that methylene is produced by the recoil process and may then exist until a collision with a bromine molecule occurs. There is considerable evidence, recently reviewed by Laidler and Casey (*J. Chem. Physics*, 1949, **17**, 1087) that methylene exists in a singlet state (all electrons paired) which is more stable than the triplet (biradical) state by at least 27 kcals./g.-mol. (Bawn and Dunning, *Trans. Faraday Soc.*, 1939, **35**, 185). Other evidence for this is based on the theoretical work of Lennard-Jones (*ibid.*, 1934, **30**, 70), and the spectrum of methylene (Herzberg, *Rev. Mod. Physics*, 1942, **14**, 195) which has been discussed by Laidler and Casey (*loc. cit.*; *J. Chem. Physics*, 1949, **17**, 213).

These facts imply that methylene should behave as an unstable molecule rather than a free radical of transient life, and that it therefore may exist in solutions of irradiated ethyl bromide until collision with bromine (or some other suitable molecule) transforms it into a more stable compound. Pearson, Purcell, and Saigh (*J.*, 1938, 409) have stated that methylene is less reactive than the methyl radical under certain conditions; this seems to be corroborated by the result shown in Table III in which it can be seen that the active methyl bromide fractions were approximately independent of the presence of bromine.

The ethyl bromide fractions will owe their large activity partly to exchange of the extractable species with ethyl bromide and partly to the reaction :

$$CH_2{\cdot}CH_2Br + Br^{\bullet}_{(recoiling)} \longrightarrow CH_2{\cdot}CH_2Br^{\bullet} + Br_{(energetic)}$$

By using the above exchange curves it is possible to show that in runs (*b*), (*c*), and (*d*), the ethyl bromide activities would have been 20—25% of the total if no exchange had occurred. This indicates that 20—25% of the active bromine atoms produced react as above; as first emphasised by Libby (*J. Amer. Chem. Soc.*, 1947, **69**, 2527), this reaction is more probable than many others in the recoil process, since a recoiling bromine atom can lose the greatest energy in a collision with an atom of the same mass, *i.e.*, a recoiling bromine atom of appreciable energy can undergo this reaction whereas collision with other (lighter) atoms present is less likely to result in the bromine atom's losing sufficient energy to enable it to combine immediately with the radicals produced.

The appreciable activities of fractions 2 and 4—7 in the presence of elementary bromine [run (*a*)] might be explained by assuming that, in the vicinity of a recoiling atom, the local concentrations of methylene, ethylene, etc., and radio-bromine are greater than those throughout the bulk of the liquid, owing to the " caging " effect of the surrounding ethyl bromide molecules (cf. Franck and Rabinovitch, *Trans. Faraday Soc.*, 1934, **30**, 120; Libby, 1947, *loc. cit.*).

As summary of the above discussion it can be stated that the results obtained with ethyl bromide are explicable if it is considered that the changes taking place occur in three stages : (i) Ejection of the recoiling radio-bromine atom which produces unstable or unsaturated molecules and may combine directly with the free radicals, etc., produced. This stage is considered to be unaffected by small concentrations of impurities present in the irradiated liquid. (ii) Diffusion of the newly-formed molecules, etc., into the bulk of the liquid. These may react further with ethyl bromide or with impurities present in small quantity, or with $HBr^{\bullet}$ or $Br{-}Br^{\bullet}$ to form non-extractable compounds. The stabilising action of free bromine is to saturate compounds containing olefinic double bonds which may be produced, thus leaving the extractable radio-bromine compounds free for subsequent extraction. In run (*a*), the number of radio active ($Br{-}Br^{\bullet}$) bromine molecules was $\sim 10^7$ and, since that of the inactive bromine present was $\sim 10^{19}$, loss of radio-bromine molecules by this mechanism may be neglected. (iii) " Exchange " between the extractable species and ethyl bromide. This is reduced by the presence of free bromine, possibly because of a lower concentration of hydrogen radio-bromide (assumed to be the exchanging agent) caused by exchange of the type :

$$HBr^{\bullet} + Br_2 \rightleftharpoons HBr + Br{-}Br^{\bullet}$$

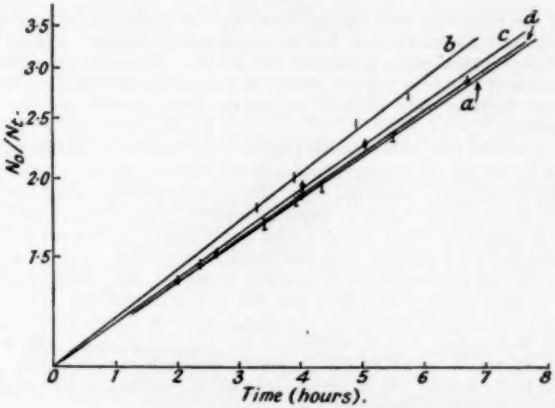
The reaction leading to the loss of extractable radio-bromine in the presence of free bromine had not yet been elucidated.

Ethylene Dibromide.—In the presence of bromine, extractions of this substance were reproducible (see Table IV) and no exchange could be detected at 15° [see Fig. 2(*a*)]. By correcting

the activities in Table IV (obtained from 3-hours irradiations) to saturation-irradiation using the formula given above but with k (the exchange constant) equal to 0, one obtains the value 48,800 ± 550. The corresponding value obtained experimentally from a specimen irradiated to saturation was 48,050 ± 450, in fair agreement with the calculated value. This indicates that no extra exchange was caused by γ-rays from the 500-mc. Ra–Be source used, though for greater γ-ray fluxes this probably does not hold (Williams, *J. Phys. Coll. Chem.*, 1948, **52**, 603).

In the absence of bromine, extractions of this substance were variable; this inconstancy is probably to be explained in terms similar to those given for ethyl bromide. It was found that aliquots of purified batches of ethylene dibromide gave results which were reproducible within the batch, but that re-purification gave results which might differ considerably from those of the first batch. Exchange occurred at 15° [Fig. 2(*b*)], and traces of ethylene present in the ethylene dibromide reduced the extractable activity; for example, extractions of an aliquot of an

FIG. 2.



a, *Natural radioactive decay.* *b*, *c*, *d*, *see text.*

|, *Purified* $CH_2Br{\cdot}CH_2Br$; I, $CH_2Br{\cdot}CH_2Br + Br$; ○, $CH_2Br{\cdot}CH_2Br + NH_2Ph$ (0·5%); +, $CH_2Br{\cdot}CH_2Br + NH_2Ph$ (4·0%).

irradiated batch gave an activity of 12,200 ± 150 for a 3-hours irradiation, but after passage of a little ethylene into another aliquot the activity extracted under the same conditions was 7900 ± 100.

TABLE IV.

(All activities refer to ethylene dibromide irradiated for 3·00 hours.)

(*a*) Concn. of Br (mg./l.).	Counts per 15 mins.	(*b*) Concn. of aniline (g./l.).	Counts per 15 mins.
50	18,400 ± 200	5	12,200 ± 150
100	18,500 ± 150	10	15,750 ± 150
100	18,300 ± 150	10	15,500 ± 150
100	18,550 ± 150	20	16,900 ± 200
100	18,600 ± 150	20	16,900 ± 200
100	18,300 ± 150	40	17,800 ± 200
		40	18,000 ± 200
		40	18,250 ± 200
		40	17,850 ± 200

Use of ethylene dibromide containing added bromine was not altogether reliable since difficulty sometimes was encountered in keeping such solutions. For example, after successful use of a specimen of ethylene dibromide for irradiations, etc., the colour of the added bromine sometines started to disappear, causing a white turbidity and formation of hydrogen bromide. When this occurred results were erratic; further addition of bromine produced more substitution, and re-stabilization of the ethylene dibromide to bromine could only be effected by careful redistillation.

In view of this, a brief examination was made of extractions of this substance containing aniline (cf. Lu and Sugden, *loc. cit.*). The aniline used was always freshly distilled in a darkened

room, since preliminary experiments showed that use of photo-decomposed aniline reduced the extractable activity considerably and made the results variable. The variation of the activities extracted (with potassium bromide solution) with aniline concentration is shown in Table IV(*b*).

Attempts were made to determine the radio-bromine present as bromoaniline, etc., by following the normal potassium bromide extraction by one with hydrochloric acid. These were not successful owing to the ease with which the activity disappeared on to the walls of the glass vessels and counters used. However, it appeared that about $16 \pm 3\%$ of the total radio-bromine was present as bromoaniline, and that this fraction was roughly independent of the aniline concentration for concentrations of 0·5—4·0. It was shown [Fig. 2(*c*) and (*d*)] that the rate of exchange between the extractable species and ethylene dibromide was reduced in the presence of aniline; curves (*c*) and (*d*) are for 10 and 40 g. of aniline per litre of ethylene dibromide. If the exchange normally proceeds by the reaction:

$$HBr^{\bullet} + CH_2Br{\cdot}CH_2Br \rightleftharpoons HBr + CH_2Br{\cdot}CH_2Br^{\bullet}$$

the inhibition of the exchange may be explained by the formation of aniline hydrobromide. This would reduce the concentration of free hydrogen radio-bromide; aniline hydrobromide is assumed to exchange much more slowly or not at all. The activity extractable was also independent of traces of ethylene present; thus, an aliquot of the specimen (mentioned above) containing ethylene together with 40 g. of aniline per litre gave an activity of $18{,}200 \pm 200$ counts per 15 minutes.

This suggests that the rôle of the added aniline is to remove all elementary radio-bromine produced, by the formation of bromoanilines and hydrogen bromide. This is consistent with the low values of the activities extracted when the concentration of aniline is small [see Table IV(*b*)]. For example, in the presence of small quantities of bromine the saturation activity is 48,800 counts/15 minutes, as shown above. This activity gives a measure of the total extractable radio-bromine produced directly from the recoil process, since there is no exchange under these conditions and the concentration of bromine is so low that direct participation by the bromine present is improbable. By correcting the activities obtained for a concentration of 10 g. of aniline per litre to saturation, by using $\tau_{effective}$ from curve (*c*) of Fig. 2, one obtains $39{,}950 \pm 650$; if this value is now multiplied by $\tau_{radioactive}/\tau_{effective}$ the resulting activity (41,850) is that which would have been obtained if no exchange had occurred. This is less than the value obtained in the presence of bromine—a result in qualitative agreement with the above explanation of the formation of bromoaniline.

As the aniline concentration is increased, the extractable activity also increases. By correction of the activities obtained with 40 g. of aniline per litre by the above method, the activity at saturation-irradiation for no exchange is found to be 48,050. The extra activity obtained must be caused by direct participation of aniline in the recoil process, as suggested by Lu and Sugden (*loc. cit.*).

It may be noted that values of the "efficiency of extraction" or "retention" have no significance when "exchange" occurs unless the time and temperature of irradiation are also specified. The importance of temperature is obvious since the activity extractable depends on the exchange which is (in general) itself temperature-dependent. The time of irradiation must also be taken into account since the rate of growth of the extractable radio-bromine is governed by its rate of disappearance ($\lambda + k$), whereas that of the total activity is governed by λ only.

Bromobenzene.—Extractions of purified specimens of bromobenzene were not reproducible except from purified batches; in the presence of bromine, extractions were reproducible and independent of the bromine concentration within the limits indicated in Table V. No exchange could be detected in either case after heating irradiated specimens (with or without bromine present) at 100° for 2 hours.

TABLE V.

Concn. of Br (mg./l.)	100	100	200	200
Activity per 15 mins. at saturation	$15{,}200 \pm 200$	$15{,}250 \pm 200$	$14{,}950 \pm 200$	$15{,}300 \pm 200$

In the light of the above results, the low efficiency of extraction in the absence of bromine might be caused by the formation of compounds containing "aliphatic" double bonds, by the addition either of molecules or of free-radicals to activated bonds in benzene rings (cf. Miller and Dobson, *J. Chem. Physics*, 1950, **18**, 865), or by the splitting of benzene rings by the recoiling atoms (cf. Stein and Weiss, *J.*, 1949, 3254). Any elementary bromine produced could then add subsequently to such unsaturated molecules; according to this explanation, the variability of

the results could be ascribed either to the incomplete saturation of such molecules by the purification process or to small amounts of hydrogen bromide present as impurity (cf. ethyl bromide).

In the presence of elementary bromine, saturation of such molecules would occur preferentially by addition of inactive bromine molecules, thus preserving the active molecules for extraction. Confirmation of the general validity of these ideas was obtained by extracting irradiated specimens of bromobenzene and then refluxing the liquid with reagents which might be expected to react with aliphatically bound bromine, but which would leave unaffected any attached to the aromatic ring. The results obtained are shown in Table VI.

TABLE VI.

[Activities correspond to counts ($\times 10^{-4}$) per 15 mins., corrected to time of removal from source and to saturation-irradiation.]

	Original state of C_6H_5Br.	Activity extracted.	Treatment.	Activity from 1st refluxing.	Activity from 2nd refluxing.	Total activity.
(*a*)	No Br present.....	713 ± 8	A	282 ± 7	25 ± 1	1020 ± 11
(*b*)	,, ...	608 ± 8	B	365 ± 5	45 ± 1	1018 ± 10
(*c*)	,, ...	604 ± 8	C	356 ± 5	59 ± 3	1019 ± 10
(*d*)	0·20 g. of Br per l. ...	869 ± 8	B	174 ± 2	38 ± 1	1081 ± 8
(*e*)	,, ,, ...	864 ± 8	C	161 ± 5	45 ± 1	1070 ± 10

A, alcoholic potassium hydroxide; B, alcoholic silver acetate; C, alcohol–zinc reduction.
Total time of treatment = 7 hours; duration of 1st refluxing = 2—2½ hrs.

It is probable that the " fixing " of the aliphatic bromine was never complete, but further reaction would have been useless since the activities obtained would have been too low to be statistically significant. In the absence of bromine it can be seen that the sum of the activity extracted and the activity obtained from the treatment was approximately constant, in agreement with the above suggestion. In the presence of bromine the same quantity was larger by about 5%; this could be caused by direct participation of the added bromine in the recoil process, although such participation seems unlikely for the reasons advanced above; an alternative explanation might be that, in the absence of bromine, compounds containing groups such as $-CH{:}CHBr^*$, etc., react only with difficulty, but that in the presence of bromine (when the double bond may be saturated) the bromine is more easily attacked by the reagents used.

In the presence of bromine, the aliphatic radio-bromine may be produced by (*a*) the disruption of benzene rings (as outlined above) by an energetic radio-bromine atom, followed by addition to the residual aliphatic radical, or (*b*) by addition of radio-bromine to an unsaturated molecule (produced by the same recoil) while these are " caged " together by the surrounding bromobenzene molecules (cf. Franck and Rabinovitch, *loc. cit.*).

Use of Organic Halides as Neutron Detectors.—Chemical aspects. All the halides studied gave results which were reproducible to $\pm 1\%$ if due attention was paid to the corrections necessitated by exchange, etc. For most purposes, perhaps, the use of ethyl iodide containing a small quantity of iodine is most convenient since reproducibility is a function only of exchange and no other complicating effects (addition of iodine to double bonds, etc.) appear to be present. Of the bromides, bromobenzene–bromine solutions are the most suitable, since the bromine remains in solution for long periods and no exchange occurs. However, if large quantities of the detecting liquid are required, the greater availability of ethylene dibromide favours its use; in this case, ethylene dibromide–bromine mixtures are the most convenient, but due care must be taken to ensure their stability. Mixtures of aniline with ethylene dibromide are less suitable, since exchange corrections must be made and also the activity extracted is dependent on the concentration and purity of the aniline.

The general method has been applied successfully in this laboratory by other authors (*e.g.*, see Parsons and Collie, *Proc. Physical Soc.*, 1950, **63**, *A*, 839), but it has been found that extraction of large quantities (5 litres) of organic halides gave erratic results caused by incomplete mixing of the halide with the sulphite extracting agent when these were shaken manually. On reducing the quantity shaken to 2·5 litres and repeating the process, results were again reproducible and the time of processing was only increased by about five minutes.

Physical aspects. For all these halides, it is necessary that the energy of the neutron fluxes to be compared is the same, since the proton- and halogen-scattering and capture cross-sections are functions of the neutron energy.

Use of ethyl iodide is convenient since the correction for saturation and decay is easily calculable, whereas with bromides this is extremely difficult owing to the number of isotopes

produced and the complexity of the decay scheme of ^{80}Br. In practice, when it is desired to compare weak neutron fluxes by using bromides, it is better to adhere to a rigorous time schedule, keeping constant the time of irradiation (unless this is done to saturation), the period between the removal of the detector from the neutron source and processing, and the time of measurement. The second of these is particularly important since the 18-minutes ^{80}Br (ground state) may also be produced in an extractable form by the decay of the excited state in organic combination; for this reason the temperature of the irradiation should also be held constant (see Segrè *et al. loc. cit.*).

Experimental.

The organic bromides were purified by redistillation, treated with elementary bromine, extracted with sodium sulphite solution, and dried ($CaCl_2$). Treatment with bromine was adopted to saturate possible olefinic impurities since these were shown to reduce the amount of extractable radio-bromine. After irradiation and extraction of a bromide, the treatment with bromine, etc., was (in general) repeated, but not the distillation. This method was adopted since often the conditions under which this method of comparing the neutron fluxes is used render a lengthy redistillation impractical. Commercial specimens of ethylene dibromide often contained olefinic impurities, the added bromine disappearing rapidly.

Neutron irradiation, and extraction and precipitation of the radio-bromine produced, were performed as described previously for ethyl iodide (Shaw and Collie, *loc. cit.*). Measurements were always made on the excited ^{80}Br isotope; this decays (half-life, 4·4 hours) with weak γ-emission into the ground state, which then decays (half-life, 18 minutes) with β and weak γ-emission. The actual radiation detected by the counter was the β-radiation of the unexcited ^{80}Br isotope in transient equilibrium with the longer-lived isomer. Each specimen was measured twice; the first count was made not less than 4 hours after extraction, in order to allow any unexcited ^{80}Br produced directly by the (n, γ) process to decay and also to establish radioactive equilibrium between the excited and the ground state. The second measurement was made about 20 hours later, in order to correct the activity for ^{82}Br (half-life, 34 hours) produced.

In general, measurements were not corrected for " self-absorption " since it was always arranged that the superficial density of the silver bromide counted corresponded to that at the maximum of the self-absorption curve (Collie, Shaw, and Gale, *Proc. Physical Soc.*, 1950, **63**, *A*, 282).

Exchange rates were measured as described for ethyl iodide (Shaw and Collie, *loc. cit.*).

Extraction efficiencies were measured by counting portions of the extracted and unextracted halide after neutron irradiation; it was found that sometimes an appreciable fraction of the extractable radio-bromine adhered to the walls of the vessel used for the irradiation; the walls of the vessel were therefore extracted separately with dilute potassium bromide solution and the radio-bromide was measured after precipitation as silver bromide.

Analyses of the Products from Irradiated Ethyl Bromide.—These were performed by adding small quantities (about 10 g.) of suitable substances as carrier and then separating them by distillation. 100 C.c. of ethyl bromide, irradiated to saturation with respect to ^{80}Br, were divided into two equal portions; these were extracted separately with aqueous potassium bromide or sodium sulphite, if free bromine was absent or present respectively. One portion was measured directly, and the other was washed with water to ensure complete removal of radio-bromide ions; the latter was then treated with bromine to saturate compounds such as vinyl radio-bromide, etc., which might be produced by the recoiling atoms. The bromine was then removed by shaking the mixture with sodium sulphite solution, and weighed quantities of methylene, ethylene, and ethylidene dibromides, and 1 : 1 : 2-tri- and 1 : 1 : 2 : 2-tetra-bromoethane were then added. The mixture was re-shaken with sulphite to ensure the removal of bromine which might have been present in the carriers, and dried over calcium chloride [Table III(*b*) and (*c*)] or anhydrous sodium sulphate [run (*d*)]. After filtration, the liquid was cooled to about $-10°$ and a weighed quantity of methyl bromide was added. All the carriers added were previously purified by redistillation and, in the case of methyl bromide, by sulphite extraction and drying over calcium chloride. The above order was adopted to minimise possible errors caused by adsorption of small quantities of some of the radio-active species present on the calcium chloride, etc., and also to ensure that no elementary bromine or hydrogen bromide was present, since in the presence of the latter exchange between the organic bromides present might have occurred during the subsequent distillation by mechanisms of the type

$$RBr^* + HBr \rightleftharpoons RBr + HBr^*$$
$$R'Br + HBr^* \rightleftharpoons R'Br^* + HBr$$

where R and R′ are alkyl or bromoalkyl.

The mixture was then distilled through a vacuum-jacketed fractionating column (20-cm. long, packed with Fenske spirals) which had been previously cooled to about $-10°$. The first fraction (methyl bromide) was collected in carbon dioxide–acetone; fractions were only collected when the temperature of a thermometer placed in the column was steady. It was advisable to cool the liquid after the ethylidene dibromide had been distilled and to continue the fractionation under reduced pressure, since otherwise " cracking " occurred and a satisfactory separation became impossible.

The various fractions (except ethyl bromide) were then weighed and diluted to 40 c.c. with alcohol and measured as described previously (Shaw and Collie, *loc. cit.*). The weights of the various substances added initially being known, corrections for the activity lost by the fractionation can be effected. Both the fractionated and the unextracted ethyl bromide were measured without previous dilution with alcohol. Since there were three different types of measurements (namely, measurements of carrier with alcohol, of

ethyl bromide, and of silver bromide obtained from the original extraction), it was necessary to convert two types of measurement into the third for comparative purposes. The equivalence between the silver bromide and the ethyl bromide counts could be established from a knowledge of the extraction efficiency of ethyl bromide containing a trace of free bromine. The conversion factor required to transform counts from the carrier (in alcohol) into those obtained from pure ethyl bromide (where "self-absorption" and β-scattering, etc., would be different) was determined experimentally by measuring a highly active specimen of ethyl bromide and a portion of it diluted with alcohol, so that the final density was equal to that of the alcoholic carrier solutions used. The errors given in Table III take into account the additional statistical errors arising from these conversions.

Conversion of "Aliphatic" Bromine Obtained from Irradiated Bromobenzene into Silver Bromide.—In each method used, the irradiated specimen of bromobenzene was extracted, washed free from radio-bromide ions, and dried ($CaCl_2$). The first method was to reflux bromobenzene with a solution of potassium hydroxide in alcohol which had been previously dried over soda-lime. After 2 hours the bromobenzene and alcohol were distilled off and the residue was acidified with nitric acid; the bromide produced was then precipitated by addition of silver nitrate, and the activity of the resulting silver bromide was measured. It was found that this process led to the formation of much more potassium bromide than expected, presumably because of reaction between the potassium hydroxide and the bromobenzene when the latter was distilled. By weighing the silver bromide produced it was possible to correct for the extra activity obtained from radio-bromine present initially in aromatic combination. The process was then repeated with the same bromobenzene and fresh alcoholic potassium hydroxide.

The second method was to reflux the irradiated bromobenzene (prepared as above) with a solution of freshly precipitated silver acetate (0·02 g.) in alcohol; after 2 hours' refluxing the alcohol and bromobenzene were distilled off and the residue was dissolved by washing it with nitric acid and then concentrated aqueous ammonia. The aqueous solutions were then mixed and acidified when necessary, and 10 mg. of potassium bromide were added; a little silver nitrate was added to ensure that this was in excess, and the silver bromide was filtered off and measured. The process was then repeated with fresh silver acetate.

The third method was to reflux bromobenzene prepared as above with zinc dust and alcohol (dried as before) for 2 hours; the zinc bromide produced was recovered by distilling off the organic liquid and dissolving the residual zinc in nitric acid containing 10 mg. of potassium bromide as carrier. The bromide was precipitated with silver nitrate and the whole process repeated.

Aniline–Ethylene Dibromide Irradiations.—These were performed as for ethyl iodide irradiations (*loc. cit.*); the aniline used was distilled in a darkened room before use. Extractions were made with water containing about 10 mg. of potassium bromide. After use, the ethylene dibromide was purified by extraction several times with hydrochloric acid and drying. The substance was then redistilled, "saturated" with bromine (as described above), and extracted with sodium sulphite solution.

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THE CLARENDON LABORATORY, OXFORD. [*Received, October 2nd,* 1950.]

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96. *Some* (n, γ) *Effects in Iodobenzene.*

By P. F. D. SHAW.

Some of the factors affecting the reproducibility of extractions (by an aqueous reagent) of radio-iodine from neutron-irradiated iodobenzene have been studied. In the presence of iodine extractions are easily reproducible, but without iodine the amount of extractable radio-iodine is variable because of the variable formation of aliphatic radio-iodine compounds which are probably produced by the "rupture" of benzene rings by the energetic recoiling radio-iodine atoms.

The low value (about 40%) for the efficiency of extraction of radio-iodine from iodobenzene compared with that for other organic monohalides is probably caused by the formation of a stabilised "iodonium" radical, Ph_2I^-. The chief evidence for this is that phenyl radicals (produced by photolysis) in iodobenzene give compounds containing the Ph–I–Ph structure, and that the presence of nitric oxide during the neutron-irradiation of iodobenzene increases the efficiency of extraction; no similar effect could be observed in bromobenzene or ethyl iodide where it is assumed that no stabilised radicals are produced.

DURING investigation (Shaw and Collie, preceding paper) of the reproducibility of extraction (by an aqueous reagent) of radio-halogens from neutron-irradiated organic halides, the Szilard–

Chalmers effect in iodobenzene was studied. Although the efficiency of extraction had previously been reported to be lower than that for other monohalides, the independence of this quantity of the presence of iodine (Lu and Sugden, *J.*, 1939, 1273) indicated that extractions of this substance might be easily reproducible and that no " exchange " corrections would be necessary (cf. McKay, *Nature*, 1937, **139**, 283).

The reproducibility of extractions of neutron-irradiated iodobenzene containing a trace of free iodine is shown in Table I (*a*) and was better than 1%. Under these conditions no exchange

TABLE I.

(*a*) Concn. of I (mg./l.).	Activity/min.*	(*b*) Concn. of Br (mg./l.).†	Activity/min.*
50	2315 ± 20	100	2325 ± 20
100	2295 ± 20	100	2305 ± 20
100	2320 ± 20		
100	2300 ± 20		
100	2320 ± 20		

* Corrected to saturation-irradiation and to time of removal from source.
† Extracting agent: sodium sulphite–potassium iodide solution.

between the extractable species and the bulk of the iodobenzene was observed after the irradiated liquid had been heated at 100° for 30 minutes before extraction.

In the absence of iodine, extractions were variable, the activities obtained being as much as 9% lower than those from iodine–iodobenzene solutions irradiated under the same conditions. Heating at 100° for 30 minutes before extraction caused a small variable decrease in the activity extracted. This did not appear to be caused by exchange between the extractable species and the iodobenzene since increasing the time of heating to 60 minutes did not further significantly lower the activity (corrected for radioactive decay). Possibly some of the extractable radio-iodine compounds add slowly to olefinic impurities produced by the recoiling atoms (see below).

The rôle of added iodine in stabilising the activities extractable seemed analogous to that of bromine in bromobenzene (Shaw and Collie, *loc. cit.*) and accordingly experiments, summarised in Table II, were performed to test the amount of aliphatic radio-iodine present: extracted neutron-irradiated specimens of iodobenzene were heated under reflux with silver acetate in alcohol. The quantity (extracted + aliphatic radio-iodine) was independent of the presence of iodine within experimental error; this indicates that, in the absence of iodine, the loss of activity from the extractable species may be caused by addition of elementary radio-iodine, etc., to compounds containing double bonds. The latter might be produced by disruption of benzene rings (as outlined for bromobenzene); the stabilising action of added iodine could then be explained by assuming that it added to such compounds, leaving the radio-iodine produced available for subsequent extraction. Confirmatory evidence was obtained from extractions of neutron-irradiated iodobenzene which contained a small quantity of added bromine [Table I (*b*)]. This bromine should saturate olefinic molecules present, and it can be seen that the activities extracted are consistent with this view since they are the same as those from iodine–iodobenzene solutions.

TABLE II.

(All activities corrected to saturation-irradiation, and to time of removal from neutron source.)

Initial state of iodobenzene.	Extracting agent.	Activity/30 mins. ($\times 10^{-6}$) (extracted).	Activity/30 mins. ($\times 10^{-6}$) (1st refluxing).	Activity/30 mins. ($\times 10^{-6}$) (2nd refluxing).	Total activity/30 mins. ($\times 10^{-6}$).
I present	Na_2SO_3	2·380 ± 0·022	0·310 ± 0·009	0·124 ± 0·010	2·814 ± 0·025
		2·375 ± 0·022	0·322 ± 0·006	0·124 ± 0·009	2·821 ± 0·025
No I present	KI	2·190 ± 0·021	0·398 ± 0·006	0·163 ± 0·009	2·751 ± 0·025

The first and the second refluxing recorded in Table II were for 30 and 60 minutes respectively; clearly the conversion of the aliphatic radio-iodine was never complete, but unfortunately further refluxing would not have given results which were statistically significant.

The aliphatic radio-iodine obtained in the presence of iodine may be produced by the direct combination of a de-energised radio-iodine atom with a " ruptured " benzene ring in the recoil process. The small variation of the activities extracted with and without free iodine present (about 9% of the total activity extracted from iodine–iodobenzene solutions), compared with the corresponding quantity (50%) for bromobenzene may be explained by the reluctance of iodine to add to double bonds, with the possible exception of " styrene-type " bonds which might be formed by the combination of " split " benzene rings and phenyl radicals in the vicinity of recoiling atoms. Such an explanation would account for the absence of a similar effect in ethyl iodide (Shaw and Collie, *J.*, 1949, 1217).

The efficiency of extraction in the presence of iodine (100 mg./l.) was 40·8 ± 1·2%. This value, though higher than that reported by Lu and Sugden (*loc. cit.*), appeared anomalously low compared with those for other organic monohalides [see Table III (*a*)], particularly when these are corrected for exchange when necessary [by multiplying by $\tau_{radioactive}/\tau_{effective}$ (see Shaw and Collie, *loc. cit.*)] in order to assess the efficiency of the direct production of extractable radiohalogen by the recoil process [Table III (*b*)].

TABLE III.

Substance (+100 mg. of free halogen/l.).	(*a*) Efficiency, %.	(*b*) Efficiency, % (corrected for exchange).	(*c*) Efficiency, % (for substance +50 mg. of halogen +100 mg. of NO/l.).*
C_6H_5I	41 ± 1	41 ± 1	49 ± 2
C_6H_5Br	56 ± 1	56 ± 2	55 ± 2
C_2H_5I	64 ± 2	65 ± 2	63 ± 2
C_2H_5Br	55 ± 2	60 ± 2	—

* See, however, Experimental section.

It is difficult to conceive that the difference between the efficiencies in bromo- and iodobenzene can be connected in any way with a difference in the nuclear properties of the two halogens, *e.g.*, in the energies of the quanta emitted on neutron capture, since one might then expect to find a similar difference in the efficiencies of ethyl iodide and bromide. This suggests that the low extraction efficiency in iodobenzene, relative to that for bromobenzene, might be caused by some chemical property of iodine which is not shared by bromine.

In bromobenzene one of the most probable " hot " reactions of energetic bromine atoms will be:

$$PhBr + Br^{*}\ (\text{recoiling}) \longrightarrow Ph^{-} + Br + Br^{*}$$

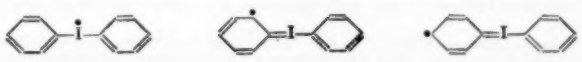
(cf. Libby, *J. Amer. Chem. Soc.*, 1947, **69**, 2523). If immediate combination of any of these radicals is not always possible owing to their high energies, it might be expected that the highly reactive phenyl radical will react with a neighbouring bromobenzene molecule as follows:

$$Ph^{-} + PhBr \longrightarrow \begin{cases} Ph{\cdot}C_6H_4Br + H \\ Ph_2 + Br \end{cases}$$

(cf. Hey, *J.*, 1934, 1966; Wieland, *Annalen*, 1934, **514**, 145).

It can be seen that the occurrence of reactions of this type will tend to increase the extraction efficiency, since combination of the radio-bromine atom (assumed to be de-energised by further collisions) with the hydrogen or bromine atoms produced will result in the formation of extractable radio-bromine compounds.

In the case of iodobenzene there appears to be an alternative fate for any free phenyl radicals produced, namely, addition to an iodobenzene molecule to form an iodonium radical. It might be expected that this would be resonant-stabilised in a way analagous to that for the diphenylmethyl radical, *i.e.*:



This might be possible for phenyl radicals in iodobenzene and not in bromobenzene because iodine can exist in a tervalent state of moderate stability as, for example, in phenyl iodochloride.

If this occurred, then two factors would tend to diminish the extraction efficiency in iodobenzene: first, the number of hydrogen and iodine atoms which might otherwise have been produced by the mechanism described above will be reduced and, secondly, there would be a chance of producing diphenyliodonium iodide molecules:

$$Ph_2I^{-} + I^{\bullet} \longrightarrow Ph_2I^{+})I^{-}$$

The latter would carry the heat of recombination and might decompose into two molecules of iodobenzene, since this substance is known to have a low thermal stability (Hartman and Meyer, *Ber.*, 1894, **27**, 502) and to decompose rapidly at about 120°.

An attempt to confirm the general validity of this argument was made by irradiating, with neutrons, iodobenzene–iodine solutions which had been previously saturated with nitric oxide. If the iodonium radicals were stabilized, the above decomposition might occur relatively slowly, being limited by the frequency of collisions between the radicals and the radio-iodine atom; in this case, combination of some of the radicals with nitric oxide molecules could occur before

such collisions; the above decomposition would therefore be reduced, and the extraction efficiency correspondingly increased. Such an effect was detected [see Table III (*b*)]; under similar conditions no increase in efficiency was obtained with bromobenzene, indicating that in this case the radicals capable of playing a rôle in the recoil process were short-lived. The ethyl iodide–nitric oxide irradiation was performed to show that the result obtained with iodobenzene was not caused by reaction between iodine atoms and nitric oxide, etc.

Evidence for the formation of the Ph–I–Ph structure under similar conditions has been obtained from the photolysis of iodobenzene by ultra-violet light. This was done while a slow stream of nitric oxide was passed through the liquid; after some time the nitric oxide was removed with hydrogen peroxide, the excess of which was destroyed with sulphur dioxide. On addition of potassium iodide, a yellow precipitate was obtained. Recrystallisation gave colourless diphenyliodonium iodide. The suggested reactions are:

$$PhI + h\nu \longrightarrow Ph^{\cdot} + I^{\cdot}$$

$$Ph^{\cdot} + PhI^{\cdot} \longrightarrow Ph_2I^{\cdot} \xrightarrow{NO} Ph_2I{\cdot}NO \xrightarrow{H_2O_2} Ph_2I^{+}\}NO_3^{-}$$

$$Ph_2I^{+}\}NO_3^{-} \xrightarrow{KI} Ph_2I^{+}\}I^{-}$$

Further evidence for the formation of the Ph_2I structure has been obtained from a specimen of iodobenzene irradiated with fast neutrons in the Harwell pile. The product contained diphenyliodonium iodide as fine crystals. Unfortunately this cannot be taken as evidence for the formation of diphenyliodonium radicals by the neutron-induced recoils, since the high γ-ray flux, with its associated secondary electrons, would also lead to a similar disruption of iodobenzene molecules.

Experimental.

Irradiations, extractions, and measurement of the iodobenzene were performed as described for ethyl iodide (Shaw and Collie, *J.*, 1949, 1217).

The transformation of the aliphatic iodine present in the irradiated material into silver iodide was carried out as described for bromobenzene (preceding paper), except that all operations were done in diffuse light to reduce photo-decomposition, and the distillations at reduced pressure to prevent production of iodine by pyrolysis in the last stages.

Neutron-irradiation of Organic Halides containing Nitric Oxide.—About 120 c.c. of the pure halide were saturated with nitric oxide (from nitric acid and copper; dried over calcium chloride; no stringent precautions were taken to exclude air). The halide (10 c.c.) was then shaken with a known amount of standard hydrogen peroxide solution and separated. The aqueous layer was titrated with standard potassium permanganate solution; the decrease in the hydrogen peroxide content was assumed to be caused by oxidation of nitric oxide to nitric acid. The amount of the nitrogen oxides present in the halides was always calculated as though nitric oxide only was present. The nitric oxide-saturated halide (100 c.c.) was then irradiated after the addition of 5 mg. of the appropriate free halogen.

After irradiation, the specimen was divided into two aliquots of which one was measured directly, and the other extracted with hydrogen peroxide and then with sodium sulphite solution before measurement. The extracted radio-halogen and an extract from the walls of the irradiation vessel were also measured to ensure that " settling " of the extractable species on the walls of the vessel had not occurred. During this treatment iodobenzene became yellow, but there was no detectable loss of nitric oxide during irradiation for 4 hours.

Production of Diphenyliodonium Iodide from the Photolysis of Iodobenzene.—Iodobenzene (40 c.c.) in a quartz vessel (diameter, 2·5 cm.) was held 1·5 cm. from a 100-w. quartz mercury-discharge tube. The whole was surrounded by a piece of metal which had been " smoked " with magnesium oxide in order to scatter some of the ultra-violet light back into the irradiation vessel. A slow stream of nitric oxide, prepared as above, was passed into the iodobenzene through a quartz delivery tube. Analysis of the solution showed that the equilibrium concentration of " nitric oxide " was approx. 0·25 g./l. (at 40°). After 3 hours the iodobenzene was shaken with hydrogen peroxide, which was then separated; the yellow peroxide layer was shaken with carbon tetrachloride to remove last traces of iodobenzene. Sulphur dioxide was passed into the peroxide layer until reduction was complete, and a few crystals of potassium iodide were added. A yellow precipitate was formed; the aqueous suspension was heated until the precipitate dissolved, and was then boiled, the yellow colour of the solution disappearing; on cooling a paler precipitate was recovered.

The whole process was repeated until enough precipitate had been obtained for analysis. The precipitate was filtered from the cooled suspension, and recrystallised twice from water and finally from alcohol (in order to ensure absence of iodide ions).

A specimen of diphenyliodonium iodide (cf. Lucas, Kennedy, and Wilmot, *J. Amer. Chem. Soc.*, 1936, **58**, 157) was purified by recrystallisation as described above. Its m. p. depended on the rate of heating, almost certainly because of decomposition (accompanied by a brown coloration) which began at about 120°. Under standard conditions the m. p. of the authentic material was 159—162°, and for the precipitate 160—162°, and the mixed m. p. was 162°. For analysis, diphenyliodonium iodide (9·74 ± 0·04 mg.; from the irradition experiment) was boiled in 5% nitric acid with a slight excess of silver nitrate, giving 5·60 ± 0·04 mg. of silver iodide (Calc. for $Ph_2I{\cdot}I$: 5·61 ± 0·02 mg.).

Under these conditions, it was found that approx. 15 mg. of diphenyliodonium iodide could be prepared for the liberation of about 50 mg. of iodine by photolysis.

On two occasions a suspension of colourless crystals, m. p. ~82° (decomp. at ~87°), was observed in the irradiated iodobenzene. They were soluble in hydrogen peroxide, and after reduction with sulphur dioxide the resulting solution gave a white precipitate on addition of potassium iodide. The quantity available did not suffice for identification as diphenyliodonium iodide, but on this assumption the original crystals were probably the 1-nitroso-derivative.

Diphenyliodonium Iodide from Pile-irradiated Iodobenzene.—The irradiated iodobenzene (5 c.c. containing free iodine) contained 9 mg. of fine crystals, insoluble in cold carbon tetrachloride, water, or alcohol, but soluble in hot water or alcohol. After recrystallisation from alcohol they melted at 157°; 1·40 ± 0·04 mg. of the substance gave 0·63 ± 0·04 mg. of silver iodide (Calc. for $Ph_2I{\cdot}I$: 0·60 ± 0·02 mg.).

The author thanks Professor Lord Cherwell, F.R.S., for laboratory facilities, Mr. C. H. Collie for much helpful discussion, and Miss E. M. W. Clarke for assistance.

THE CLARENDON LABORATORY, OXFORD. [*Received, October 2nd*, 1950.]

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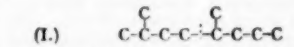
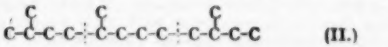
97. *Syntheses of Structural Isomers of the Terpenes. Part I.*

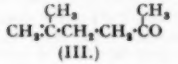
By G. R. CLEMO and B. K. DAVISON.

Syntheses of 2 : 5-dimethylocta-1 : 5-dien-8-ol and 3 : 8 : 11-trimethyldodeca-2 : 7 : 11-trien-1-ol, isomeric with geraniol and farnesol respectively, are described.

THE structures of nearly all the terpenes can be represented by the head-to-tail union of isoprene units. It is of interest therefore to examine similar systems condensed in a non-head-to-tail manner. In furtherance of this, syntheses of one representative each of types (I) and (II) have been effected, for comparison with the well-known C_{10} terpenes and C_{15} sesquiterpenes.

(I.)   (II.)

The method attempted was similar to the well-known syntheses of citral and geraniol. 2-Methylallyl chloride was condensed with ethyl acetoacetate, and the product obtained hydrolysed smoothly to 5-methylhexa-5-en-2-one (III). This ketone was then converted into the hydroxy-ester (IV) by a Reformatsky reaction and was expected to yield unsaturated ester (V; R = Et) by dehydration. Unfortunately, all the usual methods failed to eliminate water from (IV) or the corresponding acid: either a cyclic oxide (VI or VII; R = Et or H) isomeric with (IV) was obtained, or no change or decomposition took place. Analogous examples of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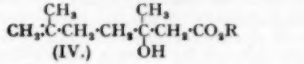
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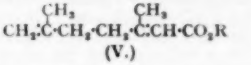
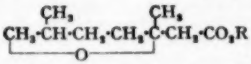
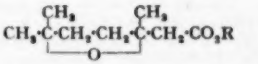

(V.)

(VI.) 

 (VII.)

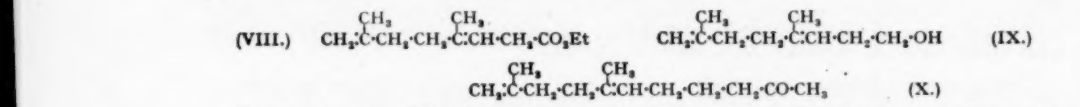
this type of ring closure are to be found in the literature: *e.g.*, Kilby and Kipping (*J.*, 1939, 435) obtained a cyclic oxide from ethyl 3-hydroxy-3 : 6 : 7-trimethyloct-6-enoate * on attempted dehydration, and Rupe and Lang (*Helv. Chim. Acta*, 1929, **12**, 1133) found that dehydrolinaloöl did not rearrange to give citral but yielded a six-membered tetrahydropyran derivative whose structure was confirmed by oxidation to the known α-cinenic acid. We have no evidence which would enable us to decide between a five- or six-membered ring structure and, as the substances obtained were useless for our main purpose, they were not investigated further.

An alternative to the Reformatsky reaction for the synthesis of αβ-unsaturated acids from ketones was provided by Heilbron, Jones, *et al.* (*J.*, 1949, 1823) in the condensation with ethoxyacetylene and subsequent rearrangement with 10% sulphuric acid. From 5-methylhex-5-en-2-one this method provided ethyl 3 : 6-dimethylhepta-2 : 6-dienoate (V; R = Et) in good yield. The derived acid was then converted into ethyl 2 : 5-dimethylocta-1 : 5-dienoate (VIII) by the Arndt–Eistert process, although in only 14% overall yield. The only other record of

* Geneva numbering (CO_2H = 1) is used throughout this paper.

the Arndt–Eistert process being applied to an αβ-unsaturated acid is that of Barnard and Bateman (*J.*, 1950, 926) who converted geranic acid into homogeranic acid, obtaining a yield of 7% from the diazo-ketone and consequently a much lower overall yield. The ester (VIII) was then reduced with lithium aluminium hydride to the corresponding alcohol (IX) which is isomeric with geraniol.

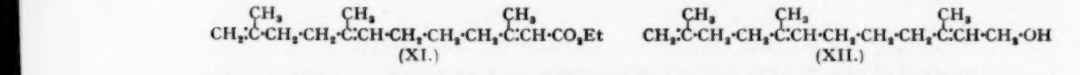
The bromide obtained from (IX) by means of phosphorus tribromide in benzene, was condensed with ethyl acetoacetate and the product hydrolysed to 2 : 5-dimethylundeca-1 : 5-dien-10-one (X), which with ethoxyacetylene gave ethyl 3 : 8 : 11-trimethyldodeca-2 : 7 : 11-trienoate (XI) and thence by reduction with lithium aluminium hydride 3 : 8 : 11-trimethyldodeca-2 : 7 : 11-trien-1-ol (XII), isomeric with farnesol.



(VIII.) (IX.)

(X.)

The C_{10} compound (IX) showed a greater likeness in odour to its naturally occurring isomer geraniol than did the C_{15} alcohol (XII) to farnesol and, like geraniol, the alcohol (IX) becomes less fragrant when kept, but it does not become discoloured. Although the position of one of



(XI.) (XII.)

the methyl groups and one of the double bonds has been altered as compared with the natural terpenes, boiling points are similar, and the refractive indices are not appreciably different.

The work is being continued.

Experimental.

(M. p.s are uncorrected.)

Ethyl 2-Methylallylacetoacetate (*2-Acetyl-4-methylpent-4-enoate*).—Ethyl acetoacetate (112 g.) was added to a boiling solution of sodium (18·4 g.) in absolute alcohol (80 ml.) in benzene (100 ml.), followed by 2-methylallyl chloride (80 ml.), and the whole refluxed for 10 hours. Excess of benzene and alcohol was partly removed, water added, and the oil taken up in ether. The aqueous layer was extracted, and the extracts were combined, washed with water, dried (Na_2SO_4), and distilled, giving an oil (123 g.), b. p. 85—86°/4—6 mm.

5-Methylhex-5-en-2-one.—The above ester (20 g.) was refluxed for 2 hours with sodium hydroxide (160 ml.; 10%), and the whole cooled, acidified (hydrochloric acid), and refluxed for a further hour, cooled again, and extracted with ether. The extract was dried (Na_2SO_4), the ether removed, and the residue distilled, giving the ketone (12 g.), b. p. 34°/4—6 mm • 150°/760 mm. The *2 : 4-dinitrophenylhydrazone*, crystallised from light petroleum (b. p. 40—60°), had m. p. 104° (Found: C, 53·3; H, 5·6. $C_{13}H_{16}O_4N_4$ requires C, 53·4; H, 5·5%). The semicarbazone, crystallised from aqueous alcohol, had m. p. 135—136° (Found: C, 56·6; H, 8·7. Calc. for $C_8H_{15}ON_3$: C, 56·8; H, 8·9%).

Ethyl 3-Hydroxy-3 : 6-dimethylhept-6-enoate.—Methylhexenone (22·5 g.), zinc wool (16 g.), dry benzene (300 ml.), and ethyl bromoacetate (30 g.) were heated under reflux until the vigorous reaction commenced. When this subsided the whole was refluxed for 3 hours, then cooled, and excess of dilute sulphuric acid added. The benzene layer was separated and dried (Na_2SO_4), the benzene removed, and the *product* distilled, giving an oil (22 g.), b. p. 97—100°/3—4 mm. (Found: C, 66·2; H, 10·4. $C_{11}H_{20}O_3$ requires C, 66·0; H, 10·0%). Microhydrogenation, using Adams's catalyst in absolute alcohol, showed that the product had one double bond.

The ethyl ester (1 g.) was refluxed with sodium hydroxide (5 ml.; 10%) for 2 hours. The *acid* was liberated with dilute hydrochloric acid and distilled in a vacuum as a very viscous liquid (0·3 g.), b. p. 132—135°/3—4 mm. (Found: C, 62·5; H, 9·0%; equiv., 175, 175. $C_9H_{16}O_3$ requires C, 62·8; H, 9·3%; equiv., 172).

Attempted Dehydration of Ethyl 3-Hydroxy-3 : 6-dimethylhept-6-enoate.—The ester (IV; R = Et) (3·35 g.) was heated with potassium hydrogen sulphate (2·25 g.) in an oil-bath at 160—180° for 3 hours. The mixture was then allowed to cool, water (10 ml.) added, and the oil extracted with ether. The ethereal extract was dried ($MgSO_4$), the solvent removed, and the residue distilled, giving an oil (1·9 g.), b. p. 69—70°/2—3 mm. (Found: C, 66·5; H, 10·0%). Microhydrogenation, using Adams's catalyst in absolute alcohol, showed the absence of a double bond.

Ethyl 3 : 6-Dimethylhepta-2 : 6-dienoate.—To well-stirred ethylmagnesium bromide [from magnesium (2·3 g.), ethyl bromide (10·9 g.), and ether (100 ml.)], ethoxyacetylene (7·4 g.) in ether (50 ml.) was added during 30 minutes and the mixture heated under reflux for 2·5 hours, an oil separating. The mixture was then cooled in a freezing mixture, and 5-methylhex-5-en-2-one (7 g.) in ether (50 ml.) added during 30 minutes with vigorous stirring, a brownish complex separating. The whole was refluxed for 1·5 hours, then cooled in a freezing mixture, the complex decomposed with ammonium chloride (20 g.) in water (100 ml.), and the ethereal layer separated. The whole was extracted with ether and the combined

ethereal liquids were shaken for 10 minutes with sulphuric acid (100 ml.; 10% w/v). The ethereal layer was separated, washed with water, dried (Na_2SO_4) and distilled, giving fractions (i) (1·7 g.), b. p. 30—42°/1—2 mm., and (ii) (7·25 g.), b. p. 64—68°/1—2 mm., and a black residue. Fraction (ii), the required *product*, decolorised bromine in water or carbon tetrachloride, gave a positive test with tetranitromethane, and was found by microhydrogenation to possess two double bonds (Found : C, 72·3; H, 9·9. $C_{11}H_{18}O_2$ requires C, 72·5; H, 9·9%).

This ester (13 g.) was refluxed with potassium hydroxide (6·5 g.) in methanol (80 ml.) for 5 hours, allowed to cool, and poured into water (120 ml.). Unhydrolysed material was extracted with ether, the residue acidified with sulphuric acid (10% w/v), and extracted with ether, and the extract dried (Na_2SO_4). After removal of the ether, the oil was distilled, giving 3 : 6-*dimethylhepta*-2 : 6-*dienoic acid* (V; R = H) (8·5 g.), b. p. 138—142°/18—19 mm. (Found : C, 69·5; H, 8·75. $C_9H_{14}O_2$ requires C, 70·1; H, 9·1%). Microhydrogenation showed that it possessed two double bonds.

The p-*bromobenzylthiuronium* salt, crystallised from alcohol, had m. p. 144—145° (Found : C, 51·2, 51·15; H, 5·8, 5·8. $C_{17}H_{23}O_2N_2SBr$ requires C, 51·2; H, 5·8%).

3 : 6-*Dimethylhepta*-2 : 6-*dienoyl Chloride*.—The foregoing acid (2 g.) in ether (2 ml.), thionyl chloride (2·3 ml.) in ether (5 ml.), and one drop of pyridine were mixed and kept at room temperature overnight. Then the excess of thionyl chloride and ether was removed, benzene was added and distilled off, and the *chloride* distilled (1·1 g.), having b. p. 93—97°/16 mm. (Found : Cl, 20·4. $C_9H_{13}OCl$ requires Cl, 20·6%).

Ethyl 3 : 6-*Dimethylocta*-2 : 6-*dienoate* (VIII).—The above acid chloride (6·3 g.) in ether (15 ml.) was added slowly, with shaking, to diazomethane (5 g.) in ether (400 ml.), cooled in a freezing mixture, and kept at room temperature overnight. The ether and excess of diazomethane were removed in a vacuum, leaving the diazo-ketone as a viscous yellow liquid. Freshly purified absolute alcohol (50 ml.) was added, the whole heated to 50—60°, and a slurry of freshly prepared silver oxide (from 40 ml. of 10% silver nitrate solution) and absolute alcohol were added gradually until the evolution of nitrogen ceased (10 hours). The whole was then refluxed for 2½ hours, charcoal added, and the mixture refluxed a further few minutes and filtered hot. The alcohol was removed from the filtrate in a vacuum and the residue distilled, giving fractions (i) (2 g.), b. p. 114—118°/18 mm. and (ii) (0·8 g.), b. p. 120—130°/18 mm., and a large tarry residue. Fraction (i) was a colourless liquid *ester*, shown by microhydrogenation to possess two double bonds (Found : C, 73·9; H, 10·5. $C_{12}H_{20}O_2$ requires C, 73·5; H, 10·2%).

3 : 6-*Dimethylocta*-2 : 6-*dien*-1-*ol* (IX).—Ethyl dimethyloctadienoate (VIII) (2 g.), in ether (5 ml.), was added dropwise to lithium aluminium hydride in ether (10 ml.; excess) and kept overnight. The excess of lithium aluminium hydride was decomposed with water, and the complex decomposed with sulphuric acid (10% w/v). The ethereal layer was separated, the residue was extracted with ether, and the extracts were combined, washed with aqueous sodium carbonate, dried ($MgSO_4$), and distilled, giving fractions (i) (0·15 g.), b. p. 66—80°/18 mm., (ii) (1·3 g.), b. p. 110—116°/18 mm., and (iii) (0·1 g.), b. p. 116—120°/18 mm. Fraction (ii) was the colourless liquid *alcohol*, n_D^{18} 1·4698, having a characteristic odour, and was shown by microhydrogenation to possess two double bonds (Found : C, 77·5; H, 11·5. $C_{10}H_{18}O$ requires C, 77·9; H, 11·7%) (cf. geraniol, n_D^{20} 1·4766).

The *diphenylurethane* recrystallised from light petroleum (b. p. 40—60°) as prisms, m. p. 80° (Found : C, 78·8; H, 7·9. $C_{23}H_{27}O_2N$ requires C, 79·1; H, 7·75%).

8-*Bromo*-2 : 5-*dimethylocta*-1 : 5-*diene*.—Phosphorus tribromide (1·4 ml.) in benzene (20 ml.) was added slowly at room temperature to the above alcohol (4 g.) in benzene (30 ml.), the mixture was kept overnight, then poured on ice, and the benzene layer separated, washed with sodium carbonate solution, and distilled, giving a colourless *bromide* (1·8 g.), b. p. 90—96°/18 mm., which quickly became brown in the air (Found : C, 55·9; H, 8·1; Br, 36·1. $C_{10}H_{17}Br$ requires C, 55·4; H, 7·85; Br, 36·9%). The derived *thiuronium picrate*, recrystallised from alcohol, had m. p. 138° (Found : C, 45·7; H, 5·4. $C_{17}H_{22}O_7N_4S$ requires C, 46·1; H, 5·2%).

Ethyl 2-*Acetyl*-6 : 9-*dimethyldeca*-5 : 9-*dienoate*.—Ethyl acetoacetate (2·7 g.) was run into sodium ethoxide [from sodium (0·3 g.) and ethanol (3 ml.)] in benzene (5 ml.) and refluxed for 0·5 hour. Then the above bromide (2·4 g.) in benzene (5 ml.) was added, the whole refluxed for 36 hours and then allowed to cool, water (20 ml.) added, and the benzene layer separated. Solvent and excess of ethyl acetoacetate were removed in a vacuum and the product distilled, giving a small fore-run and the *keto*-ester as an oil (1·4 g.), b. p. 160—180°/18 mm., which was unsaturated (tetranitromethane) (Found : C, 71·95, 72·4; H, 9·9, 9·7. $C_{16}H_{26}O_3$ requires C, 72·25; H, 9·8%).

7 : 10-*Dimethylundeca*-6 : 10-*dien*-2-*one* (X).—The above ester (1·4 g.) was refluxed for 4 hours with methanolic potassium hydroxide (1·4 g. in 14 ml.), most of the methanol removed, water added, and the whole acidified (hydrochloric acid), refluxed for a further 2 hours, cooled, and extracted with ether. The extract was dried ($MgSO_4$), the solvent removed, and the product distilled, giving fractions (i) (1·0 g.), b. p. 70—78°/1 mm. (bath-temp., 100°), and (ii) (0·2 g.), b. p. 100—120°/1 mm. (bath-temp., 140—160°). Fraction (i), the colourless *ketone*, was unsaturated (Found : C, 80·7; H, 11·2. $C_{13}H_{22}O$ requires C, 80·4; H, 11·3%), and microhydrogenation showed that it possessed two double bonds. Fraction (ii) was a different *substance* (Found : C, 72·55; H, 10·25. $C_{16}H_{26}O_3$ requires C, 72·25; H, 9·8%). An attempted preparation of the 2 : 4-dinitrophenylhydrazone, using 2 : 4-dinitrophenylhydrazine sulphate in ethanol, gave only a dark red oil.

Ethyl 3 : 8 : 11-*Trimethyldodeca*-2 : 7 : 11-*trienoate* (XI).—The above ketone (0·9 g.) in ether (5 ml.) was added dropwise to a stirred suspension of ethoxyethynylmagnesium bromide [from magnesium (0·18 g.) and ethoxyacetylene (0·53 g.)] in ether (5 ml.), the whole refluxed for 4½ hours, then cooled, and the complex decomposed with ammonium chloride (5 g.) in water (15 ml.). The ethereal layer was

separated and the residue extracted with ether. From the combined extracts, the solvent was removed, the product taken up in methanol (7 ml.) containing 10 drops of sulphuric acid (10% w/v), set aside at room temperature for 30 minutes, poured into water (20 ml.), and extracted with ether. The extract was dried, the solvent removed, and the product distilled, giving an *ester* (0·4 g.), b. p. 70—80°/1 mm. (bath-temp., 140—160°), which decolourised bromine in water or carbon tetrachloride (Found: C, 77·6; H, 10·6. $C_{17}H_{28}O_2$ requires C, 77·3; H, 10·6%).

3 : 8 : 11-*Trimethyldodeca*-2 : 7 : 11-*trien*-1-*ol* (XII).—The ester (XI) (0·3 g.) in ether (4 ml.) was added to lithium aluminium hydride in ether (2 ml.; 90 vols.) and left overnight. Excess of lithium aluminium hydride was decomposed with water, and the complex with sulphuric acid (10% w/v). The ethereal layer was separated, the residue was extracted, and the combined extracts and ethereal layer were washed with aqueous sodium carbonate, dried ($MgSO_4$), and distilled, giving a colourless ***alcohol*** (0·2 g.), b. p. 60—70°/1 mm. (bath-temp., 120—140°), n_D^{18} 1·4845 (Found: C, 81·5; H, 12·1. $C_{15}H_{26}O$ requires C, 81·1; H, 11·7%). The product was unsaturated and microhydrogenation showed it to possess three double bonds. The *diphenylurethane* crystallised from light petroleum (b. p. 60—80°) as needles, m. p. 110° (Found: C, 80·1; H, 8·2. $C_{28}H_{31}O_2N$ requires C, 80·6; H, 8·4%).

One of us (B. K. D.) thanks the Department of Scientific and Industrial Research for a maintenance grant, and we thank Imperial Chemical Industries Limited for a gift of methylallyl chloride.

UNIVERSITY OF DURHAM, KING'S COLLEGE,
NEWCASTLE-ON-TYNE, 1.

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98. *The Chemistry of the Triterpenes. Part VII.* An Inter-relationship between the Lupeol and the β-Amyrin Series. Elucidation of the Structure of Lupeol.*

By T. R. AMES, T. G. HALSALL, and E. R. H. JONES.

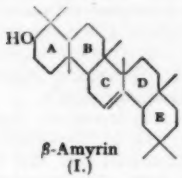
Two of the three major groups of triterpenes have been inter-related. Lupeol derivatives can be isomerised by acid treatment into compounds of the δ-amyrenol series; the relationship of these compounds to the corresponding β-amyrin derivatives, from which they are formed by acid-induced isomerisations, is reasonably well established. Compounds of the β-amyrin and lupeol series are identical in rings A, B, C, and D, except for the presence of the ethylenic bond in ring C in the β-amyrin series and a possible stereochemical difference at $C_{(18)}$, *i.e.*, the junction of rings D and E. If structure (I) is accepted for β-amyrin then it follows, from the results described in this paper, that lupeol must be represented by formula (IV). A preliminary account of this work has already been published (Ames and Jones, *Nature*, 1949, **164**, 1090).

IN the last twenty years, largely because of the brilliant and extensive researches of Ruzicka and his school, rigorous relationships have been established between a large majority of the well-characterised pentacylic triterpenoid compounds and one or other of three parent $C_{30}H_{50}O$ alcohols, α-amyrin, β-amyrin, and lupeol. (For summaries, see Spring, *Ann. Reports*, 1941, **38**, 192, and Noller, *Ann. Rev. Biochem.*, 1945, **14**, 383.) Hitherto it has not been possible to effect any interconversions between these parent compounds, but both β-amyrin and lupeol have now been transformed into common intermediates by reactions capable of structural interpretation.

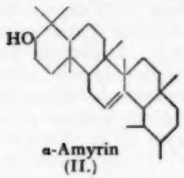
On the basis of a considerable volume of degradative evidence obtained with a number of the triterpenes of the β-amyrin series, the structure (I), originally suggested for β-amyrin by Haworth (*Ann. Reports*, 1937, **34**, 327), has now been established with a considerable degree of certainty (cf. Bischof, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1949, **32**, 1911). For α-amyrin, which is similar in many respects to the β-isomer, the closely related structure (II) has been

* The following are regarded as constituting the earlier members of this series: Part I. Lupanetriol and its Oxidation. *J.*, 1940, 456. Part II. The Oxidation of Lupenyl Esters. *J.*, 1940, 1335. Part III. The Constitution of Lupeol. *J.*, 1941, 757. Part IV. Surface Films of Lupane Derivatives. *J.*, 1941, 761. Part V. Optical-rotatory Power and Structure in Triterpenoid Compounds. Application of the Method of Molecular-rotation Differences. *J.*, 1944, 659. Part VI. The Degradation of Lupeol Derivatives to C_{27}-Ketones. *Rec. Trav. chim.*, 1950, **69**, 368.

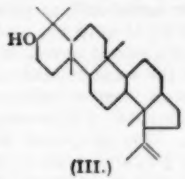
proposed (Meisels, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1949, **32**, 1075), and convincing evidence has recently been adduced (*idem*, *ibid.*, 1950, **33**, 700) concerning the identity in rings



β-Amyrin
(I.)



α-Amyrin
(II.)



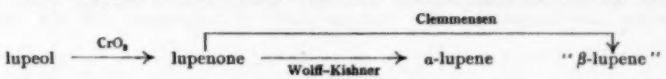
(III.)

A and B of α- and β-amyrin. At first sight it is rather difficult to believe that some of the differences observed between the amyrins arise from the minor structural variation in ring E, but a major stereochemical difference, *i.e.*, at the D—E ring junction, may be involved (cf. Meisels, Jeger, and Ruzicka, *ibid.*, 1950, **33**, 700).

The properties of lupeol and the other members of this group of pentacyclic triterpenes differ sharply in certain respects from those of the α- and the β-amyrins. Thus, in contrast to the latter, lupeol does not afford 1 : 8-dimethylpicene, 1 : 2 : 7-trimethylnaphthalene, or 2 : 7-dimethylnaphthalene on selenium dehydrogenation (Ruzicka, Further, Pieth, and Schellenberg, *Helv. Chim. Acta*, 1937, **50**, 1564) and therefore does not possess a hydropicene carbon-skeleton. Another major differentiation is to be found in the molecular-rotation differences (Barton and Jones, *J.*, 1944, 659) (see Table II). Although it has been shown that the secondary hydroxyl group in lupeol is in a similar environment to that in the amyrin series (Ruzicka, Jeger, and Huber, *Helv. Chim. Acta*, 1945, **28**, 942), the unsaturated centre is quite differently situated, being present in lupeol in a readily hydrogenated *iso*propenyl side-chain (Ruzicka and Rozenkranz, *Helv. Chim. Acta*, 1940, **23**, 1311; Jones and Meakins, *J.*, 1940, 1335). Surface-film measurements (Bilham, Jones, and Meakins, *J.*, 1941, 761) indicate that this *iso*propenyl grouping is attached at the opposite end of the pentacyclic system from the secondary hydroxyl group. The evidence available hitherto has permitted only tentative suggestions to be made concerning the structure of lupeol, with formula (III) finding most favour and providing explanations for the majority of the reactions. The results now to be discussed are best interpreted on a slight modification (IV) of this formula, the angular methyl group being sited at the alternative position at the junction of rings D and E.

Attempts to investigate the structure of ring E of lupeol, following stepwise degradation of the side-chain, have been disappointing (Jones and Meakins, *J.*, 1941, 757; Ruzicka, Huber, and Jeger, *Helv. Chim. Acta*, 1945, **28**, 195; cf. Davy, Jones, and Halsall, *Rec. Trav. chim.*, 1950, **69**, 368). Since only very poor yields of the C_{27} pentacyclic ring ketones could be obtained, it was clear that no really worthwhile progress could be expected from this approach, and that a completely new direction of attack had to be found. It seemed that this might be possible by transforming lupeol or its derivatives into isomeric compounds more susceptible to study by conventional degradative methods.

Some evidence already existed that the double bond in lupeol could migrate under the influence of acidic reagents since Heilbron, Kennedy, and Spring (*J.*, 1938, 329) had found that



lupenone, which gave α-lupene on Wolff–Kishner reduction, yielded an isomeric "β-lupene" on Clemmensen reduction. This isomer, produced only in very poor yield, presumably by acidic isomerisation, was regarded as a pure compound but it now seems that it was possibly an impure specimen of the lupene-I, described below. Further evidence of rearrangement involving the

lupeol ⟶ lupeol hydrochloride ⟶ *iso*lupeol

double bond was provided by Duerden, Heilbron, McMeeking, and Spring (*J.*, 1939, 322), who showed that lupeol could be converted into an *iso*lupeol (obtained as its acetate), by addition of hydrogen chloride to the double bond followed by dehydrochlorination and acetylation.

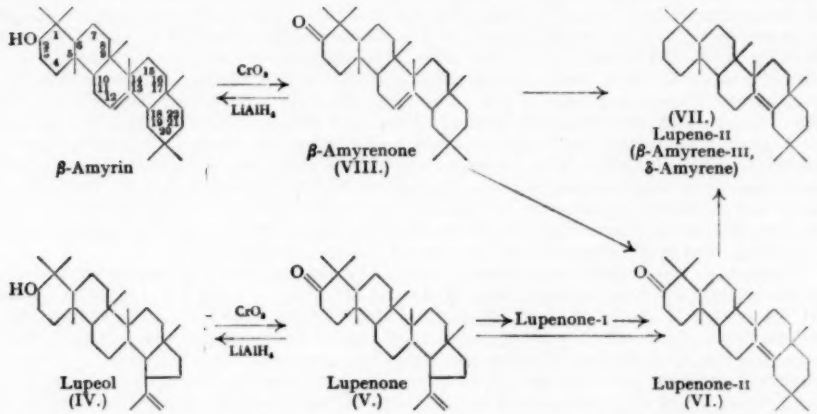
Stimulated by these possibilities, but hardly encouraged by the yields obtained and difficulties encountered by the earlier workers, a systematic study of the influence of acidic

reagents on lupeol derivatives was begun. After a prolonged investigation of the reaction conditions with various lupeol derivatives it has been found possible to convert lupenone (V) into an isomer, lupenone-I, in over 40% yield, by treatment with a solution (*ca.* 6%) of sulphuric acid in acetic acid at room temperature for 4 days. Treatment of lupenone with a solution (*ca.* 15%) of sulphuric acid in benzene–acetic acid at room temperature for 15 days gave a 40% yield of a second isomer, lupenone-II (VI). Lupenone-I has also been converted into lupenone-II under the same conditions. Concentration of acid, rather than time of reaction, appears to determine whether lupenone-I or lupenene-II is formed in the isomerisation reaction.

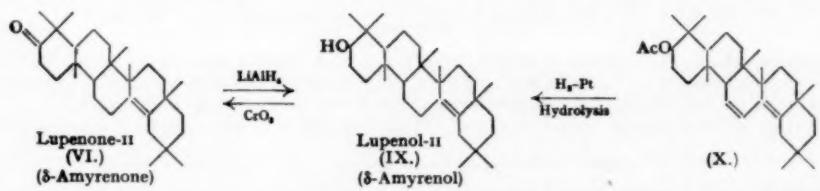
Reduction of lupenone-II by the Wolff–Kishner procedure gave a hydrocarbon, lupene-II (VII). This compound has been shown to be identical with β-amyrene-III (δ-amyrene; see later), prepared from β-amyrenone (VIII) by reduction with amalgamated zinc and hydrochloric acid according to Winterstein and Stein (*Annalen*, 1933, **502**, 223). The constants for the products obtained by the alternative routes are compared in Table I; no melting-point depression was observed with a mixture of lupene-II and β-amyrene-III, and their infra-red spectra, determined in suspension in "Nujol," were indistinguishable.

Isomerisation of β-amyrenone (VIII) in benzene solution with sulphuric acid in acetic acid also gave lupenone-II (VI) (δ-amyrenone—see later), whose melting point was undepressed on admixture with lupenone-II prepared from lupenone. Identical 2 : 4-dinitrophenylhydrazones were obtained from the ketones prepared by the two routes (cf. Table I).

Reduction of lupenone-II with lithium aluminium hydride gave an alcohol, lupenol-II (IX), with physical constants identical with those of δ-amyrenol (see Table I) (Ruzicka and Jeger,



Helv. Chim. Acta, 1941, **24**, 1243; Ruzicka, Jeger, and Norymberski, *Helv. Chim. Acta*, 1942, **25**, 457), the structure of which seems to be indicated from its preparation from the dienyl acetate (X) (cf. Barton and Brooks, *J. Amer. Chem. Soc.*, 1950, **72**, 3314) by partial hydrogenation and hydrolysis. The melting point of δ-amyrenol was not depressed by



admixture with lupenol-II. Comparisons were also made between the corresponding acetates and benzoates. Oxidation of δ-amyrenol with chromic acid gave δ-amyrenone, which, as already indicated, had the same physical constants as, and gave no depression in melting point on admixture with, lupenone-II (see Table I).

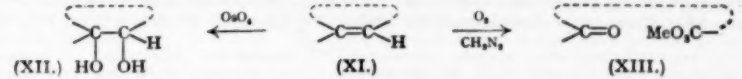
TABLE I.

	Observed. M. p.	Observed. $[\alpha]_D^{20}$.	Literature. M. p.	Literature. $[\alpha]_D^{20}$.
(1) Lupenone-II (from lupenone)	199·5—202·5°	−12°	—	—
(2) Lupenone-II (from β-amyrenone)	200 —202·5	−12	—	—
(3) δ-Amyrenone (from δ-amyrenol)	199·5—201	−12	—	—
2 : 4-Dinitrophenylhydrazone of (1)	222 —224	+22	—	—
2 : 4-Dinitrophenylhydrazone of (2)	222 —223	+19	—	—
2 : 4-Dinitrophenylhydrazone of (3)	223 —224	+21	—	—
(4) Lupene-II (from lupenone)	191·5—192	−33·5	—	—
(5) β-Amyrene-III (from β-amyrenone) [1]	191·5—192·5	−32·5	187 —189·5°	−22°
(6) Lupenol-II (from lupenone)	212 —212·5	−50·5	—	—
(7) δ-Amyrenol (from β-amyrin) [2]	211·5—213·5	−49·5	213 —213·5	−52
(8) Acetate of (6)	207·5—209	−34	—	—
(9) Acetate of (7) [2]	208·5—209·5	−34	208·5—209·5	−35
(10) Benzoate of (6)	225 —226·5	− 7·5	—	—
(11) Benzoate of (7) [2]	225 —227	—	224 —225	− 8

[1] Winterstein and Stein, *loc. cit.* [2] Ruzicka and Jeger, *loc. cit.*

Since the identities of δ-amyrenol and lupenol-II, and δ-amyrenone and lupenone-II, have been established and since these compounds contain the β-amyrin carbon-skeleton, the amyrin nomenclature is obviously to be preferred to that based on lupenone-II, but both nomenclatures are used in this paper in order to indicate the source of the compound under discussion. As has already been indicated, the structure of δ-amyrenol (lupenol-II) can be regarded as established by the work of Ruzicka and Jeger (*loc. cit.*). The oxidation of δ-amyrenol to δ-amyrenone by chromic acid leads to structure (VI) for lupenone-II (δ-amyrenone) provided no isomerisation of the double bond occurred during the oxidation. That this is so follows from the reduction of δ-amyrenone back to δ-amyrenol by lithium aluminium hydride, wherein no rearrangement of the double bond would be expected to occur (cf. Shoppee and Summers, *J.*, 1950, 687; Koller, Dietrich, and Jeger, *Helv. Chim. Acta*, 1950, **33**, 1050). The major products of the reduction of β-amyrenone and lupenone with this reagent are β-amyrin and lupeol, respectively. These results indicate that the hydroxyl group at $C_{(3)}$ in β-amyrin has the same configuration as that at $C_{(3)}$ in δ-amyrenol and in lupeol. From formula (VI) for lupenone-II, structure (VII) follows for lupene-II (β-amyrene-III), it being generally understood that ethylenic-bond migrations do not occur on Wolff–Kishner reduction other than in αβ-unsaturated carbonyl compounds. The results described in the following paper provide additional confirmation that no rearrangements occur during this reduction. Structure (VII) receives confirmation from the infra-red spectrum of lupene-II, which is compatible with the presence of a tetra-substituted double bond, which can only be present in the 13 : 18-position.

Wolff–Kishner reduction of lupenone-I gives lupene-I, which is also obtained by the direct isomerisation of α-lupene with sulphuric acid in acetic acid–benzene or ethanol. Lupene-I can also be prepared directly from lupenone (V) by reduction under Clemmensen conditions. The infra-red spectrum of this new hydrocarbon (partial formula XI) shows a strong band at 800 cm.$^{-1}$, suggestive of the presence of a trisubstituted double bond. A similar band appears in the spectra of α-pinene, Δ^5-cholestene, and analogously substituted olefins. Lupene-I is



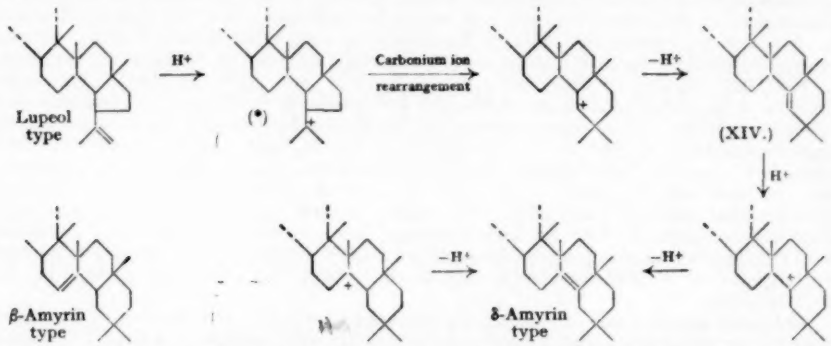
(XII.) (XI.) (XIII.)

converted by treatment with osmic acid into a diol (XII), which forms only a monoacetate. Ozonolysis of lupene-I gave no significant amounts of low molecular-weight carbonyl compounds, indicating that the ethylenic bond is in a ring, and the acidic fraction of the ozonolysis product gave, after esterification with diazomethane, a keto-ester, $C_{31}H_{52}O_3$ (XIII). This did not form ketonic derivatives, but the presence of the keto-group was clearly indicated by its absorption in the ultra-violet region.

Reduction of lupenone-I with lithium aluminium hydride yielded an alcohol, lupenol-I, from which the acetate and benzoate were prepared. It was found possible to obtain lupenyl-I acetate directly from lupenyl acetate, albeit in poor yield, by isomerisation of the latter in benzene solution with sulphuric acid in glacial acetic acid. The poor yield was not unexpected

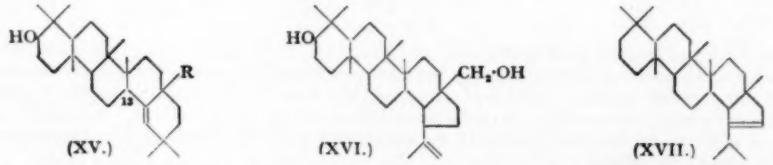
as we have found that the acetoxy-group of triterpene acetates is rather unstable under the acidic conditions used for the isomerisations described. Attempts to isomerise lupenyl-I acetate or lupenyl acetate directly to δ-amyrenyl acetate were not very successful but in one experiment δ-amyrenyl acetate was isolated from the isomerisation products resulting from lupenyl acetate. This result is significant because it provides additional evidence that the hydroxyl group at $C_{(3)}$ in the lupeol series has the same configuration as that at $C_{(3)}$ in the β-amyrin series. This identity of configuration has already been indicated by the lithium aluminium hydride reduction of β-amyrenone and lupenone to β-amyrin and lupeol, respectively.

At the present time it is not possible to put forward unique structures for the compounds of the lupene-I series. Structure (XIV) is not inconsistent with the evidence given above, and it fits conveniently into the picture as an intermediate in the mechanism indicated below for the conversion from the lupeol series into the δ-amyrin series. This mechanism involves rearrangements which are already familiar in terpene and steroid chemistry. However, recent work by Barton and Brooks (*loc. cit.*) has provided convincing evidence that structure (XIV) must be ascribed to the triterpene germanicol (full structure, XV; R = Me) (Simpson, *J.*, 1944, 283). Lupenol-I and germanicol are not identical, and hence structure (XIV) could not represent the lupene-I series unless lupenol-I and germanicol are stereoisomeric at $C_{(13)}$. That this is not the case has now been shown by Davy, Halsall, and Jones, *Chem. and Ind.*, 1950, 732) by the conversion of betulin (XVI), a member of the lupeol group which must have the same configuration at $C_{(13)}$ as lupenol-I, into moradiol (XV; R = CH_2·OH) (Barton and Brooks, *loc. cit.*) belonging to the germanicol group. If the above mechanism is correct, germanicol derivatives should be isomerised by acidic reagents into compounds of the lupene-II type. Since no germanicol derivatives have yet been isolated from the products of the isomerisation of lupenone to lupenone-II, it is believed that such derivatives probably isomerise under less



drastic conditions than those necessary for the conversion of lupenone into lupenone-II. Indeed some evidence of this possibility in a more complicated case has been provided by David (cf. *Bull. Soc. chim.*, 1950, **17**, 169). This point is under investigation.

It is believed that the lupene-I type skeleton is formed as a result of the carbonium ion (•) being capable of undergoing other transformations in addition to those postulated in the above mechanism, that these other transformations lead to lupene-I and its derivatives, and that,



under suitable conditions, as in the formation of lupenone-II from lupenone-I, these transformations are reversible. Further work on the structure of lupene-I and its derivatives is in progress. One of the structures being considered is (XVII).

These results lead to the conclusion that the structures of rings A, B, C, and D of lupeol and

β-amyrin are identical apart from the presence of the double bond at the 12 : 13-position in β-amyrin and a possible difference in stereochemical configuration at $C_{(18)}$. They further indicate that, if β-amyrin has structure (I), then lupeol has the structure (IV), since it is only possible to formulate a reasonable mechanism for the formation of δ-amyrin derivatives if structure (IV) is correct. Various other structures which have been suggested for lupeol would give rise to compounds other than δ-amyrin derivatives on isomerisation.

TABLE II.

	Alcohol	Acetate (1)	Benzoate (2)	Ketone (3)	Δ_1	Δ_2	Δ_3
α- and β-Amyrin [1] group	—	—	—	—	+ 6	+145	+ 60
Lupeol–betulin [1] group ...	—	—	—	—	+70	+200	+140
Lupenol-I	+400	+444	+572	+534	+44	+172	+134
δ-Amyrenol [2]	−216	−161	− 41	− 51	+55	+175	+165

[1] Barton and Jones, *loc. cit.*

[2] The figures given are the average of those determined in the present study and by Ruzicka and Jeger (*loc. cit.*).

Although it would not be wise to attach much significance to the values at this stage, the molecular-rotation differences associated with lupenol-I and δ-amyrenol are listed in Table II, where they are compared with those of the α- and β-amyrin and lupeol groups.

EXPERIMENTAL.

(All melting points were determined on a Kofler block and are corrected, unless specifically stated. Rotations were determined in chloroform. Light petroleum refers to the fraction with b. p. 40—60° unless otherwise stated.)

*Lupene-*I.—(a) *Isomerisation of α-lupene.* (i) α-Lupene (1 g.) in benzene (15 c.c.) was treated at room temperature with a mixture of acetic acid (45 c.c.) and sulphuric acid (3·5 c.c.; *d* 1·84). The solution rapidly became brown, and the temperature rose to 40°, thus preventing immediate precipitation of α-lupene. After 5 days at 20°, dilution with water and isolation with ether yielded a brown resin (1·13 g.). This was dissolved in benzene (10 c.c.)–light petroleum (10 c.c.) and adsorbed on to a column of alumina (50 g.; activity I—II). Elution with light petroleum (400 c.c.) afforded *lupene-*I, crystallising from ethyl acetate as platelets (360 mg.; 36%), m. p. 208—210°, $[\alpha]_D^{20}$ +82° (*c*, 1·20). Several recrystallisations from ethyl acetate and from chloroform–methanol raised the m. p. to 224·5—225·5°, $[\alpha]_D^{20}$ +102° (*c*, 1·10) (Found: C, 87·5; H, 11·9. $C_{30}H_{50}$ requires C, 87·75; H, 12·25%). In the Liebermann–Burchard test, a deep-red colour was obtained; with tetranitromethane, a yellow colour.

(ii) α-Lupene (3 g.) in benzene (75 c.c.) was refluxed with ethanolic sulphuric acid (375 c.c.; 15%) for 48 hours. After cooling to 0°, the separated solid was purified by chromatography and crystallised from ethyl acetate, giving platelets, m. p. 213—214° (210 mg.; 7%). The melting point was raised by several recrystallisations from ethyl acetate and chloroform–methanol to 223—224°, undepressed on admixture with lupene-I prepared by method (b).

(b) *Clemmensen reduction of lupenone.* Amalgamated zinc (60 g.) was covered with a solution of lupenone (8 g.) in acetic acid (300 c.c.) and water (40 c.c.). The solution was refluxed with concentrated hydrochloric acid (55 c.c.), a further five portions (30 c.c. each) being added over a period of 8½ hours. The solution was diluted with water, and the product was isolated by repeated ethereal extraction. Evaporation of the washed and dried extract, followed by careful addition of methanol, afforded lupene-I (770 mg.; 10%), m. p. 200—203° (capillary), $[\alpha]_D$ +86° (*c*, 1·25). The melting point was raised to 223—224° by several recrystallisations from ethyl acetate and chloroform–methanol.

*Lupenone-*I.—Lupenone (3 g.) in acetic acid (50 c.c.) was treated with a mixture of acetic acid (10 c.c.) and sulphuric acid (5 c.c.; *d* 1·84). The solution was kept at 20° for 96 hours, by which time it had developed a green fluorescence and deposited clusters of needles. These were recrystallised from chloroform–methanol giving needles of *lupenone-*I (1·49 g.; 50%), m. p. 187—192°, raised to 217·5—218·5° by several recrystallisations from chloroform–methanol; $[\alpha]_D^{20}$ +126° (*c*, 2·82) (Found: C, 84·75; H, 11·35. $C_{30}H_{48}O$ requires C, 84·8; H, 11·4%). Light absorption in chloroform–ethanol (1 : 4): Maximum, 2860—2920 A.; ε = 30·5. The Leibermann–Burchard reagent gave a brown colour. More lupenone-I (*ca.* 15% yield) was isolated by dilution and ethereal extraction of the residual reaction mixture, followed by chromatographic purification of the solid obtained from the ether extract.

*Lupenone-*I 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol–benzene as orange needles, m. p. 266—267° (decomp.) (Found: N, 9·2. $C_{36}H_{52}O_4N_4$ requires N, 9·3%).

*Lupenone-*II.—(*a*) Lupenone (5 g.) in benzene (50 c.c.) was treated with a mixture of glacial acetic acid (425 c.c.) and sulphuric acid (75 c.c.; *d* 1·84). The solution was warmed to 50° and then kept at 20° for 15 days. The resultant brown solution (green fluorescence) was poured into water, and the resinous product, isolated with ether, was dissolved in benzene (20 c.c.), adsorbed on a column of alumina (350 g.; activity I—II), and eluted first with light petroleum (750 c.c.), and then with light petroleum–benzene (1 : 1) (900 c.c.). The material (2·81 g.) obtained from this second eluate was recrystallised from ethanol–acetone (1 : 1) yielding *lupenone-*II as platelets (2·1 g.; 42%), m. p. 181—188° raised by many recrystallisations from acetone–methanol and chloroform–methanol to 199·5—202·5°, $[\alpha]_D^{20}$ −12° (*c*, 1·05) (Found: C, 84·8; H, 11·7. $C_{30}H_{48}O$ requires C, 84·8; H, 11·4%). Light absorption in chloroform–ethanol (1 : 4): Maxima, 2430, 2510, 2620 (inflexion), and 2870—2920 A.; ε = 1000,

1000, 1000 (all approx.), and 33, respectively. The band at 2870—2920 A. shows the presence of a ketonic grouping. The bands at 2430, 2510, and 2620 A. indicate the presence of a small amount (*ca.* 3—4%) of a diene impurity, probably the ketone corresponding to β-amyradienol-II which shows these same maxima (Green, Mower, Picard, and Spring, *J.*, 1944, 527). In the Liebermann–Burchard test a deep reddish-purple colour was obtained. The behaviour of lupenone-II on the Kofler block was very characteristic, as it partly melted and then assumed a new crystal form (needles) at 170—190° before melting finally at the temperature given. *Lupenone*-II 2 : 4-*dinitrophenylhydrazone* crystallised from chloroform–methanol as platelets, m. p. 222—224°, $[\alpha]_D^{20}$ +22° (*c*, 0·98) (Found : N, 9·4. $C_{36}H_{52}O_4N_4$ requires N, 9·3%). Light absorption in ethanol : Maximum, 3700—3720 A.; ε = 25,000.

(*b*) Lupenone-I (500 mg.) was treated exactly as for the preparation of lupenone-II from lupenone. The resinous product obtained after 15 days' storage at 20° was adsorbed on a column of alumina (70 g.; activity I—II) and fractionally eluted with benzene–light petroleum (1 : 1). A fraction (0·35 g.) was obtained which crystallised from acetone–ethanol as platelets, m. p. 199—202° undepressed on admixture with a specimen of lupenone-II prepared from lupenone; it had $[\alpha]_D^{20}$ −2·5° ± 5° (*c*, 0·237). Insufficient material prevented further purification.

(*c*) β-Amyrenone (1·3 g.) in benzene (13 c.c.) was treated with acetic acid (110 c.c.) and sulphuric acid (19·5 c.c.; *d* 1·84). The solution was warmed to 80° and then kept at 20° for 14 days. The resultant reddish-brown solution was worked up as in method (*a*) above, except that benzene was used as the extractant in order to avoid emulsification. Elution of the product from alumina (100 g.; reactivated; activity I) with light petroleum–benzene (2 : 3) (500 c.c.) gave a partially crystalline product (981 mg.) which, after several recrystallisations from ethanol and acetone–methanol, gave lupenone-II as flat needles, m. p. 200—202·5° undepressed on admixture with a specimen prepared from lupenone by the method described above; it had $[\alpha]_D^{20}$ −12° (*c*, 1·39). The 2 : 4-dinitrophenylhydrazone, which crystallised as platelets from chloroform–methanol, had m. p. 222—223°, undepressed on admixture with the 2 : 4-dinitrophenylhydrazone described above, $[\alpha]_D^{20}$ +19° (*c*, 0·42).

Hydrogenation of Lupene-I.—Lupene-I (16·3 mg.) in ethyl acetate–acetic acid (1 : 1) (10 c.c.) was shaken in a microhydrogenation apparatus with pre-reduced Adams's platinum catalyst (16·1 mg.) and hydrogen for 44 hours at 20° (Found : uptake of hydrogen, 0·87 c.c. Required for 1 double bond : 0·89 c.c.) The saturated *hydrocarbon* formed crystallised from ethyl acetate as platelets, m. p. 232—233°, $[\alpha]_D^{20}$ +26° (*c*, 0·57) (Found : C, 87·6; H, 12·35. $C_{30}H_{52}$ requires C, 87·3; H, 12·7%). The hydrocarbon gave no colour with tetranitromethane.

Hydroxylation of Lupene-I.—Lupene-I (770 mg.) in dry pyridine (21 c.c.) and dry chloroform (25 c.c.) was treated with osmic acid (470 mg.), and the solution was kept at 20° for 26 days. The resulting dark solution was evaporated to dryness under reduced pressure at 60°, and the residue was refluxed with mannitol (3 g.) in ethanol (20 c.c.), benzene (10 c.c.), and sodium hydroxide solution (10 c.c.; 2N.) for 10 hours. Dilution with water and isolation with benzene yielded a solid which was fractionated on a column of alumina (activity I—II). A fraction, eluted with ether, afforded a *diol* (474 mg.; 62%) crystallising from ethyl acetate as platelets, m. p. 288—291°, $[\alpha]_D^{20}$ +12° (*c*, 1·79) (Found : C, 80·75; H, 11·55. $C_{30}H_{52}O_2$ requires C, 81·0; H, 11·8%). The diol (130 mg.) was acetylated in dry pyridine (3 c.c.) at 20° with acetic anhydride (1 c.c.) for 20 hours. The product (120 mg.) gave, on crystallisation from methanol, platelets of a *monoacetate*, m. p. 264—265·5°, $[\alpha]_D^{20}$ −8° (*c*, 1·97) (Found : C, 78·7; H, 10·9. $C_{32}H_{54}O_3$ requires C, 78·95; H, 11·2%).

Wolff–Kishner Reduction of Lupenone-I.—Lupenone-I (1·2 g.) was heated in an autoclave for 5 hours at 175° and 100 atmospheres with hydrazine hydrate (7·8 c.c.; 60%) and a solution of sodium (1·5 g.) in ethanol (30 c.c.). After the reduction the mixture was diluted with water, and the precipitated solid was isolated; it crystallised from ethyl acetate as platelets (0·9 g.; 75%), m. p. 222—223° undepressed on admixture with a specimen of lupene-I prepared by the isomerisation of α-lupene.

Wolff–Kishner Reduction of Lupenone-II.—Lupenone-II (720 mg.) was heated in an autoclave for 7 hours at 200° and 50 atmospheres with hydrazine hydrate (2 c.c.; 60%) and a solution of sodium (0·88 g.) in ethanol (18·7 c.c.). The product crystallised from methanol–chloroform as platelets (552 mg.; 77%), m. p. 191·5—192°, $[\alpha]_D^{20}$ −33·5° (*c*, 1·11). The m. p. was undepressed on admixture with a specimen of β-amyrene-III prepared from β-amyrenone by Winterstein and Stein's method (*loc. cit.*). The infra-red spectra of lupene-II and β-amyrene-III were identical.

Ozonolysis of Lupenone-I.—Lupenone-I (1·0 g.) in acetic acid (50 c.c.) (redistilled from chromic acid) was treated with a stream of ozonised oxygen (6%) for 3 hours (= 4·5 mol. of O_3), the exit gases being passed through two wash-bottles containing water. The reaction mixture was then steam-distilled until 400 c.c. of distillate had been collected. The formaldehyde content of the combined distillate and washings was estimated as formaldehyde dimedone, m. p. 186—187° undepressed on admixture with an authentic specimen (yield of the dimedone : 16·6 mg., 2·4%). Lupenone under comparative conditions gave 26 and 22% yields of formaldehyde.

Ozonolysis of Lupene-I.—Lupene-I (1 g.) in chloroform (100 c.c.) was treated with a stream of ozonised oxygen (6%) for 5½ hours at 10°. The chloroform was removed at 0° and the residue steam-distilled. The distillate, together with the aqueous washings of the ozoniser exit gases, was treated with 2 : 4-dinitrophenylhydrazine sulphate solution. No precipitate resulted. The residue from the steam-distillation gave an acidic fraction (0·79 g.) which was esterified with diazomethane in ethereal solution. The crude ester was chromatographed on alumina (70 g.; reactivated; activity I); elution with benzene gave the *keto-ester* (0·45 g.; 39%), which crystallised from methanol as needles, m. p. 184—186°, $[\alpha]_D$ +17° (*c*, 0·42) (Found : C, 78·95; H, 10·7. $C_{31}H_{52}O_3$ requires C, 78·75; H, 11·1%). Light absorption in chloroform–ethanol (1 : 4) : Maximum, 2700—2790 A.; ε = 37·5. The ester gave no colour with the Liebermann–Burchard reagent, nor did it form a 2 : 4-dinitrophenylhydrazone under the normal conditions.

Reduction of β-Amyrenone.—β-Amyrenone (500 mg.) in anhydrous tetrahydrofuran (30 c.c.) was treated at 20° with a solution of lithium aluminium hydride in dry ether (2·85 c.c.; 0·375M.). Next morning the complex was decomposed with excess of sulphuric acid (2N.) with ice-cooling. Further dilution with water, followed by isolation of the product in the usual manner, and crystallisation from chloroform–methanol gave needles of β-amyrin (273 mg.; 55%), m. p. 197—199° undepressed on admixture with an authentic specimen, $[\alpha]_D$ +91° (*c*, 1·23). (Literature values for β-amyrin: m. p. 197—197·5°, $[\alpha]_D^{20}$ +88·4°.)

Reduction of Lupenone.—Lupenone (350 mg.) was reduced with lithium aluminium hydride, as above, giving lupeol, which crystallised from acetone as needles (210 mg.; 60%), m. p. 209—212°, $[\alpha]_D$ +33° (*c*, 0·41). Three recrystallisations from acetone raised the m. p. to 214—215°, undepressed on admixture with an authentic specimen, $[\alpha]_D$ +28·5° (*c*, 2·15). [Literature values for lupeol: m. p. 215—216°, $[\alpha]_D^{20}$ +26·4° (*c*, 3·51).]

Reduction of Lupenone-I.—Lupenone-I (365 mg.) was reduced with lithium aluminium hydride as above, giving *lupenol-I*, crystallising from chloroform–methanol as platelets (219 mg.; 60%), m. p. 253—254°, $[\alpha]_D$ +94° (*c*, 1·37) (Found: C, 84·25; H, 11·7. $C_{30}H_{50}O$ requires C, 84·4; H, 11·8%). Acetylation gave *lupenyl-I acetate*, which separated from methanol–chloroform as platelets, m. p. 243—244°, $[\alpha]_D^{20}$ +95° (*c*, 1·01) (Found: C, 82·05; H, 11·0. $C_{32}H_{52}O_2$ requires C, 82·0; H, 11·2%). Benzoylation of lupenol-I with benzoyl chloride in pyridine gave *lupenyl-I benzoate*, which crystallised from methanol–chloroform as platelets, m. p. 273—275°, $[\alpha]_D^{20}$ +108° (*c*, 1·375) (Found: C, 83·65; H, 10·5. $C_{37}H_{54}O_2$ requires C, 83·7; H, 10·25%).

Reduction of Lupenone-II.—Lupenone-II (500 mg.) was reduced with lithium aluminium hydride as above, giving lupenol-II, which crystallised from methanol as needles (368 mg.; 74%), m. p. 212—212·5° undepressed on admixture with δ-amyrenol prepared from β-amyradienol-II by Ruzicka and Jeger's method (*loc. cit.*), $[\alpha]_D^{20}$ −50·5° (*c*, 2·00). Acetylation of lupenol-II gave lupenyl-II acetate, which crystallised from chloroform–methanol as platelets, m. p. 207·5°—209° undepressed on admixture with δ-amyrenyl acetate, $[\alpha]_D^{20}$ −34° (*c*, 0·37). Benzoylation of lupenol-II with benzoyl chloride in pyridine gave lupenol-II benzoate, which crystallised from chloroform–methanol as platelets, m. p. 225—226·5° undepressed on admixture with δ-amyrenyl benzoate, $[\alpha]_D^{20}$ −7·5° (*c*, 0·65).

δ-Amyrenone.—δ-Amyrenol (200 mg.), prepared from β-amyrin, was dissolved in acetic acid (40 c.c.)–chloroform (5 c.c.) and treated at 20° with a solution of chromic acid (70 mg.) in 95% acetic acid (5 c.c.). The mixture was kept for 16 hours, and the product was then isolated by dilution of the solution with water, and ethereal extraction. Crystallisation from chloroform–methanol gave platelets (25 mg.; 63%), m. p. 197—199°, $[\alpha]_D$ −9° (*c*, 1·03). Repeated recrystallisation from acetone–methanol gave platelets of δ-amyrenone, m. p. 199·5—201° undepressed on admixture with lupenone-II, $[\alpha]_D^{20}$ −12° (*c*, 1·06). The δ-amyrenone showed the characteristic melting-point behaviour of lupenone-II. Light absorption in chloroform–ethanol (1 : 4): Maxima, 2510, 2625 (inflexion), and 2900 A.; ε = 500, 400, and 30, respectively. As in the case of lupenone-II derived from lupenone the spectrum shows the existence of a ketonic grouping and indicates the presence of a small amount (*ca.* 1—2%) of a diene impurity. δ-Amyrenone 2 : 4-dinitrophenylhydrazone crystallised from chloroform–methanol as platelets, m. p. 223—224° undepressed on admixture with lupenone-II 2 : 4-dinitrophenylhydrazone, $[\alpha]_D^{20}$ +21° (*c*, 1·12). Light absorption in ethanol: Maximum, 3700—3720 A., ε = 25,000.

Isomerisation of Lupenyl Acetate.—(*a*) Lupenyl acetate (1·5 g.) in benzene (30 c.c.) was treated with a mixture of concentrated sulphuric acid (12 c.c.) and acetic acid (120 c.c.), and the solution was kept at 20° for 40 hours. It was then diluted with water, and a yellow solid was isolated by ethereal extraction. This was dissolved in benzene (10 c.c.) and adsorbed on a column of alumina (150 g.; activity I—II). Elution with light petroleum–benzene (1 : 1) (500 c.c.) gave a solid (800 mg.) which was crystallised from acetone–methanol as platelets, m. p. 227—230° raised by several further recrystallisations (with heavy loss of material) to 244—245° and then undepressed with an authentic specimen of lupenyl-I acetate prepared from lupenone-I. It had $[\alpha]_D^{20}$ +93° (*c*, 1·65).

(*b*) (With Mr. G. S. Davy). Lupenyl acetate (5 g.) was dissolved in benzene (25 c.c.) and a mixture of acetic acid (350 c.c.) and concentrated sulphuric acid (80 c.c.) was added. After 8 days at 20° about one-third of the solution (175 c.c.) was worked up, excess of water being added, and the aqueous solution extracted with benzene. The extract yielded a solid (0·92 g.) which was dissolved in benzene–pentane (1 : 1) and adsorbed on a column of alumina (60 g.; activity I). From the fifth 100-c.c. fraction eluted with benzene–light petroleum (1 : 1), a solid (60 mg., $[\alpha]_D^{20}$ +14°, was obtained. This was recrystallised twice from chloroform–methanol, giving flat needles, m. p. 208—208·5°, $[\alpha]_D^{20}$ −20° (*c*, 0·5). A mixture with authentic δ-amyrenyl acetate, m. p. 209—209·5°, melted at 208—208·5°. These data indicate that the solid is essentially δ-amyrenyl acetate.

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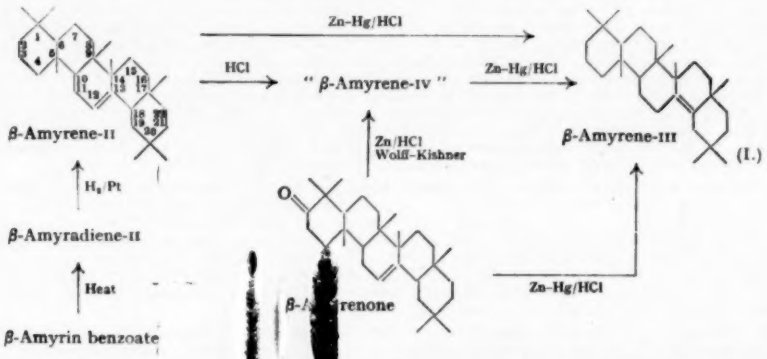
99. *The Chemistry of the Triterpenes. Part VIII. The α- and β-Amyrenes.*

By G. S. Davy, T. G. Halsall, and E. R. H. Jones.

A review of the chemistry of the α- and β-amyrenes in the light of current structures for α-amyrin, β-amyrin, and lupeol indicated a number of anomalies. These have been investigated and resolved. In the course of the investigations it has been found that the conditions which give rise to the isomerisation of the double bond in derivatives of β-amyrin have no effect upon the double bond in those of α-amyrin.

In the investigations leading to the discovery of the inter-relationship of the β-amyrin and lupeol groups of triterpenes described in the preceding paper, the $C_{30}H_{50}$ hydrocarbon, β-amyrene-III, was obtained from both groups. This compound was first obtained by Winterstein ond Stein (*Annalen*, 1933, **502**, 233) by the reduction of β-amyrenone with amalgamated zinc and hydrochloric acid and also by the isomerisation of β-amyrene-II with the same reagents. The β-amyrene-II was prepared by hydrogenation of β-amyradiene-II (β-amyrilene-II), obtained by pyrolysis of β-amyrin benzoate.

β-Amyrene-III (δ-amyrene) is now known (see preceding paper) to be the parent hydrocarbon of δ-amyrenol (Ruzicka and Jeger, *Helv. Chim. Acta*, 1941, **24**, 1243), with the structure indicated (I). β-Amyrene-II should be the parent hydrocarbon of β-amyrin, with the ethylenic linkage in the 12 : 13 position, its formation from β-amyradiene-II being the result of the hydrogenation of the double bond formed on pyrolysis of the benzoate. This is probably a *cis*-elimination of benzoic acid, not involving a structural rearrangement (*cf.* Barton, *J.*, 1949



2174). The formation of β-amyrene-III from β-amyrene-II can be imagined as proceeding *via* a carbonium ion as indicated in the preceding paper, and from β-amyrenone by the same mechanism, the isomerisation accompanying the reduction of the carbonyl group. If this mechanism is correct then the conversion of β-amyrene-II into β-amyrene-III should be able to proceed in the presence of acid alone and should not require the presence of amalgamated zinc. Indeed, Winterstein and Stein found that β-amyrene-II could be isomerised in the presence of hydrochloric acid alone, but the product they obtained was not β-amyrene-III, but an isomer, " β-amyrene-IV," with an optical rotation lying approximately midway between those of β-amyrene-II and -III. β-Amyrene-IV was also obtained by Winterstein and Stein by reduction of β-amyrenone with pure zinc and hydrochloric acid, and they record that it could be isomerised further by amalgamated zinc and hydrochloric acid to β-amyrene-III.

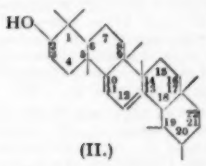
Ruzicka, Schellenberg, and Goldberg (*Helv. Chim. Acta*, 1937, **20**, 791) have also reported the preparation, from β-amyrenone by Wolff–Kishner reduction, of a compound which is said to be probably identical with β-amyrene-IV. This conversion and the reactions described by Winterstein and Stein are indicated in the accompanying reaction scheme, in which are given the structures which are now acceptable for β-amyrenes-II and -III and for β-amyrenone. It is clear that the formulation of any structure for β-amyrene-IV, as an intermediate in the con-

version of β-amyrene-II into β-amyrene-III, is well-nigh impossible. This anomaly became very obvious during the course of the work described in the preceding paper and a reinvestigation of the reactions involved seemed to be highly desirable.

β-Amyrene-II was obtained by hydrogenation of β-amyradiene-II, prepared according to Winterstein and Stein's method, and its constants agreed with those previously reported. Repetition of the reduction of β-amyrenone by the procedure used by Ruzicka *et al.* (*loc. cit.*) and also by a modified Wolff–Kishner method, resulted in the formation in both cases, not of β-amyrene-IV, but of β-amyrene-II, with constants identical with those of the β-amyrene-II prepared from β-amyradiene-II. This result was in accord with our expectation that no isomerisation would occur under the conditions of Wolff–Kishner reductions.

A reinvestigation of the isomerisation of β-amyrene-II in glacial acetic acid, hydrochloric acid being used alone as the catalyst, in the absence of zinc or mercury, showed that if the isomerisation was carried to completion, β-amyrene-III was the sole product. (The β-amyrene-III had a rotation of $[\alpha]_D$ −33° as compared with the figure of −22° reported by Winterstein and Stein. We believe that this is due to our product being purer.) If, however, the isomerisation was not carried to completion products of variable rotation were obtained, with some of the rotations corresponding to those reported for the supposed β-amyrene-IV. It was also found that as the isomerisation proceeded the rotation of the products gradually fell. These results lead to the conclusion that Winterstein and Stein's so-called " β-amyrene-IV " was a mixture of β-amyrene-II and β-amyrene-III. They also show that neither zinc, nor mercury, is necessary for the acid-induced isomerisation of β-amyrene-II to β-amyrene-III, thus confirming the ideas implicit in the mechanism proposed for the formation of β-amyrene-III. Further confirmation is provided by the acid-induced isomerisation of β-amyrenone to δ-amyrenone, when only the double bond is affected, and the Wolff–Kishner reduction of the carbonyl group of the δ-amyrenone giving β-amyrene-III, described in the preceding paper.

In view of the conversion of β-amyrenone into δ-amyrenone, described in the preceding paper, and the discovery by Winterstein and Stein of the formation of β-amyrene-III by Clemmensen reduction of β-amyrenone, it was of interest to study comparable reactions with α-amyrenone, since the structure (II) which has been suggested for α-amyrin (Meisels, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1949, **32**, 1075; 1950, **33**, 700) admits of the possibility of double-bond migration analogous to that observed in the β-amyrin series.



(II.)

Winterstein and Stein have already described a Clemmensen reduction of α-amyrenone and report the formation of α-amyrene-II, which is also obtained by hydrogenation of α-amyradiene-II, the diene obtained by the pyrolysis of α-amyrin benzoate. They further report that α-amyrene-II is a mixture of two α-amyrenes, one melting at 120—122° ($[\alpha]_D$ +98·9°) and the other melting at 110—112° ($[\alpha]_D$ +88·8°). Whilst the isolation of two α-amyrenes from the Clemmensen reduction can easily be explained by assuming isomerisation of the 12 : 13 double bond, the production of the same two α-amyrenes by hydrogenation of α-amyradiene-II is difficult to understand. The hydrocarbon corresponding to the structure (II) for α-amyrin should be obtainable by the Wolff–Kishner reduction of α-amyrenone. This reaction has already been carried out by way of the semicarbazone by Ruzicka, Muller, and Schellenberg (*Helv. Chim. Acta*, 1939, **22**, 758) who isolated a hydrocarbon, m. p. 124°, $[\alpha]_D$ +95°, which they considered to be identical with the higher-melting form of α-amyrene-II obtained by Winterstein and Stein.

We have carried out a Wolff–Kishner reduction of α-amyrenone *via* the hydrazone and obtained the same hydrocarbon, and it is also produced by the Clemmensen reduction of α-amyrenone. No form melting at *ca.* 110° was obtained. Repetition of Winterstein and Stein's procedure for the preparation of α-amyrene-II gave this compound as platelets which, under the microscope, were observed to melt partially at 115°, the melt then crystallised in short needles which melted at 123·5—124°. There were no depressions of melting point on admixture of this compound and the products from α-amyrenone. It is clear, therefore, that there is only one compound, α-amyrene-II, formed from α-amyrin benzoate by pyrolysis and hydrogenation, and from α-amyrenone either by Wolff–Kishner or Clemmensen reduction, but that the hydrocarbon is dimorphic. The results also reveal the important fact that the double bond in α-amyrin is not isomerised under the conditions of the Clemmensen reduction. Attempts to isomerise the double bond in α-amyrenone using the conditions which have been found to isomerise β-amyrenone to δ-amyrenone proved unsuccessful, α-amyrenone being recovered in

good yield after treatment in benzene solution with sulphuric acid in acetic acid for 15 days. The use of more drastic conditions have, as yet, led only to extensive degradation of the α-amyrenone.

The absence of isomerisation provides yet another example of the extraordinary lack of reactivity shown by the double bond of α-amyrin, as compared with that of β-amyrin. Meisels, Jeger, and Ruzicka (*loc. cit.*) ascribe this lack of reactivity to steric hindrance by the methyl group sited at C_{19}. As indicated in the preceding paper, however, it is possible that α- and β-amyrin possess different configurations at C_{18} and that this difference accounts, in part, at least, for the difference in reactivity of the double bonds of the two compounds.

Experimental.

(Rotations were measured in chloroform. Melting points were determined on the Kofler block and are corrected.)

*β-Amyrene-*II.—(a) *From β-amyradiene-*II. β-Amyradiene-II (500 mg.) (Winterstein and Stein, *loc. cit.*) was hydrogenated for 45 minutes at 20° in acetic acid (30 c.c.)–ethyl acetate (10 c.c.), Adams's platinum oxide (50 mg.) being used as catalyst. Water was then added and the product isolated by benzene extraction. Crystallisation from ethyl acetate–methanol gave needles (350 mg.), m. p. 159—162° raised by further recrystallisation from acetone and from chloroform–methanol to 160—162·5°, $[\alpha]_D^{20}$ +96° (*c*, 0·803).

(b) *From β-amyrenone by Wolff–Kishner reduction.* (i) β-Amyrenone semicarbazone (400 mg.) was added to sodium ethoxide, prepared from sodium (0·75 g.) in absolute ethanol (10 c.c.), and the mixture was heated for 20 hours at 185° in a small autoclave. The product (400 mg.) was isolated by benzene extraction. It was dissolved in pentane and chromatographed on a column of neutral alumina (50 g.; activity I). The column was washed with pentane (60 c.c.), and a fraction (350 mg.) was then obtained, by elution with pentane (70 c.c.), which, on crystallisation from chloroform–methanol, gave needles of β-amyrene-II, m. p. 161—162·5° undepressed on admixture with authentic β-amyrene-II, $[\alpha]_D^{20}$ +95·5° (*c*, 1·28). (ii) β-Amyrenone (700 mg.) was added to sodium ethoxide, prepared from sodium (700 mg.) and absolute ethanol (15 c.c.), and 60% aqueous hydrazine hydrate (5 c.c.), and heated for 6 hours at 180—200° in a small autoclave. When cool, excess of water was added giving a precipitate which was filtered off and dried. This was dissolved in chloroform, the solution was filtered through activated charcoal, and methanol was added to the filtrate which deposited needles (455 mg.), m. p. 159—160°, when kept. The needles (120 mg.) were dissolved in pentane (10 c.c.) and chromatographed on alumina (20 g.; activity I). Elution with pentane (35 c.c.), after washing the column with the same eluent (25 c.c.), gave a fraction (120 mg.) which was crystallised from chloroform–methanol giving needles of β-amyrene-II, m. p. 162—163° undepressed on admixture with authentic β-amyrene-II, $[\alpha]_D^{20}$ +96·5° (*c*, 1·16).

*Action of Hydrochloric Acid–Acetic Acid on β-Amyrene-*II.—(*a*) β-Amyrene-II (47 mg.) was dissolved in acetic acid (20 c.c.), and concentrated hydrochloric acid (8 c.c.) was slowly added to the warm solution. The mixture was refluxed for 16 hours and, after it had cooled, excess of water was added. The product was isolated by benzene extraction, and was crystallised from chloroform–methanol, giving short needles (31 mg.), m. p. 185—188°, $[\alpha]_D^{20}$ −19° (*c*, 1·03). Three recrystallisations from the same solvent gave β-amyrene-III, m. p. 190—191° undepressed on admixture with authentic β-amyrene-III, $[\alpha]_D^{20}$ −33° (*c*, 0·46).

(*b*) β-Amyrene-II (50 mg.) was dissolved in warm acetic acid (20 c.c.), and concentrated hydrochloric acid (8 c.c.) was added. After the mixture had been heated under reflux for 15 minutes, excess of water was added and the product isolated by benzene extraction. Crystallisation from chloroform–methanol gave needles (15 mg.), m. p. 157—161°, $[\alpha]_D^{20}$ +38° (*c*, 0·503). The value of the specific rotation suggested that the needles were a mixture of β-amyrene-II (55%) and β-amyrene-III (45%). A synthetic mixture of β-amyrene-II (55%) and β-amyrene-III (45%) melted at 157—160·5°, after crystallisation from chloroform–methanol. Recrystallisation of the melt from the same solvent gave needles, m. p. 157—159°.

*α-Amyrene-*II.—(a) *Hydrogenation of α-amyradiene-*II. α-Amyradiene-II (210 mg.) (Winterstein and Stein, *loc. cit.*) was dissolved in acetic acid (30 c.c.)–ethyl acetate (10 c.c.) and hydrogenated for 30 minutes at 20°, Adams's platinum oxide being used as catalyst. The product was crystallised from acetone giving platelets of α-amyrene-II (96 mg.), m. p. 112·5—123° (112—113° capillary). Further crystallisations gave platelets melting partially at 115°, after which the melt crystallised in short needles, m. p. 123·5—124°, $[\alpha]_D^{20}$ +97° (*c*, 0·80).

(b) *Wolff–Kishner reduction of α-amyrenone.* α-Amyrenone (1 g.) was added to 60% aqueous hydrazine hydrate (5 c.c.) and sodium ethoxide, prepared from sodium (0·7 g.) dissolved in absolute ethanol (15 c.c.), and the mixture was heated at 200—230° for 6 hours in a small autoclave. Dilution with water, and benzene extraction gave a product (755 mg.) which was dissolved in pentane (10 c.c.) and chromatographed on a column of neutral alumina (40 g.; activity I). Elution with pentane gave an oil (440 mg.) which was crystallised from ethyl acetate–chloroform–methanol giving platelets, m. p. 116—118°. Three recrystallisations from acetone gave α-amyrene-II, m. p. 123—124° undepressed on admixture with an authentic specimen, $[\alpha]_D^{20}$ +95° (*c*, 1·13).

(c) *Clemmensen reduction of α-amyrenone.* α-Amyrenone (1 g.) was dissolved in acetic acid (50 c.c.) with warming, zinc amalgam (7 g.) and concentrated hydrochloric acid (20 c.c.) were added, and the mixture was refluxed for 16 hours. The product, isolated with benzene, was dissolved in pentane and chromatographed in a column of neutral alumina (30 g.; activity I). Elution with pentane gave

an oil, crystallisation of which from chloroform–ethyl acetate–methanol gave platelets (450 mg.), m. p. 110—111°. These were dissolved in pentane (10 c.c.) and rechromatographed on a column of alumina (20 g.; activity I). Elution with pentane gave a fraction (325 mg.) which, after two crystallisations from acetone, yielded α-amyrene-II, m. p. 123—124° undepressed on admixture with an authentic specimen, $[\alpha]_D^{20}$ +94° (*c*, 0·67).

The Action of Sulphuric Acid–Acetic Acid on α-Amyrenone.—α-Amyrenone (500 mg.) was dissolved in benzene (5 c.c.), and a mixture of acetic acid (40 c.c.) and sulphuric acid (8 c.c.; *d* 1·84) was added with shaking. The mixture was kept at 20° for 15 days and then diluted with water, and the product isolated by benzene extraction. The product was dissolved in light petroleum (15 c.c.; b. p. 40—60°) and chromatographed on a column of alumina (50 g.; activity I). Elution with benzene–light petroleum (b. p. 40—60°) (2 : 1) gave 430 mg. of crystalline material. Recrystallisation of this from chloroform–methanol gave unchanged α-amyrenone, m. p. 125—126° undepressed on admixture with an authentic specimen, $[\alpha]_D^{20}$ +109° (*c*, 1·3).

Attempted Isomerisation of α-Amyrenone by using Vigorous Conditions.—α-Amyrenone (520 mg.) was dissolved in benzene (5 c.c.), and a mixture of acetic acid (40 c.c.) and sulphuric acid (8 c.c.; *d* 1·84) was added with shaking. The mixture was kept at 80° for 17 hours. The cooled, deep magenta solution was diluted with water, and the product isolated by ethereal extraction. The product (520 mg.) was dissolved in *n*-pentane–benzene (3 : 2) and chromatographed on a column of alumina (40 g.; activity I) Several fractions were obtained by elution, successively, with pentane–benzene (3 : 2), pentane–benzene benzene, ether, and ether–ethanol (95 : 5). None of the fractions could be crystallised, all remaining as oils or resins.

One of the authors (G. S. D.) is indebted to the University of Manchester for a post-graduate scholarship.

THE UNIVERSITY, MANCHESTER, 13. [*Received, October 5th*, 1950.]

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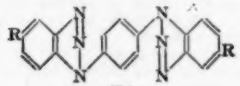
100. *Experiments on the Preparation of Indolocarbazoles. Part III.*

By P. V. CLIFTON and S. G. P. PLANT.

Investigations into the possibility of applying established synthetical methods in the carbazole group to the preparation of indolocarbazoles from derivatives of *p*-phenylenediamine, including 3-aminocarbazole and related substances, have culminated in the synthesis of 6-cyanoindolo(2′ : 3′-3 : 4)-carbazole.

THIS communication describes attempts to apply known methods for the synthesis of carbazoles to the preparation of indolocarbazoles from various derivatives of *p*-phenylenediamine. Manjunath (*J. Indian Chem. Soc.*, 1927, **4**, 271) was unable to obtain an indolocarbazole by heating the phenylenebistriazole (I; R = H), and we have confirmed his observations. The degree of success attending the Graebe–Ullmann reaction, however, can vary widely among closely related compounds, and it seemed desirable to investigate other substances of this type. Accordingly the bistriazoles (I; R = Cl, OMe, and CN) have been synthesised and then heated under a variety of conditions, but none gave the desired product.



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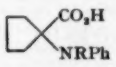

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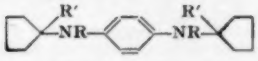
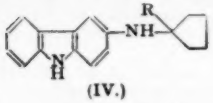


(III.)

Carbazole has been obtained from 1-anilino*cyclo*pentane-1-carboxylic acid (II; R = H), and the 1- and 3-methylcarbazoles from the corresponding toluidino-compounds, by heating them with potassium hydroxide, sometimes with the addition of sodium ethoxide (Plant and Facer, *J.*, 1925, **127**, 2037; Oakeshott and Plant, *J.*, 1926, 1210; 1927, 484), and it seemed possible that the same reaction might be applied to the acid (III; R = H, R′ = CO_2H) with the formation of an indolocarbazole. *NN′*-Di-(1-cyano*cyclo*pentyl)-*p*-phenylenediamine (III; R = H, R′ = CN) has been prepared by adding potassium cyanide to *p*-phenylenediamine and *cyclo*pentanone in acetic acid, and converted into the corresponding diamide. When the latter

was fused with potassium hydroxide, a substantial amount of *p*-phenylenediamine was formed, and the fact that the alkali residue was completely soluble in water showed the absence of an indolocarbazole. In this respect the diamide behaves like the analogous compound derived from tolylene-2 : 4-diamine (Bond, Deegan, and Plant, *J.*, 1949, S160). Hydrolysis of the diamide led to the acid (III; R = H, R′ = CO_2H), which, on fusion with a mixture of potassium hydroxide and sodium ethoxide, gave 3-aminocarbazole. Evidently carbazole formation has proceeded in one half of the molecule, but fission of the type which characterises the diamide has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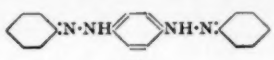
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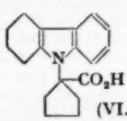
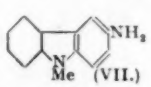

(VI.)

ensued in the other, and the acid (IV; R = CO_2H) may be an intermediate stage in the process. In an attempt to prepare (IV; R = CO_2H), 3-(1-cyano*cyclo*pentylamino)carbazole (IV; R = CN) has been made, but hydrolysis to the acid has not been effected. Boiling hydrochloric acid gave 3-aminocarbazole, and the use of concentrated sulphuric acid to obtain the amide led to sulphonation.

Several possibilities exist for the application of the Fischer indole synthesis to this problem in the *p*-phenylene series, and some of these have been examined. Unfortunately, we have been unable to eliminate $2NH_3$ from *N′N‴*-di*cyclo*hexylidene-*p*-phenylenedihydrazine (V), and we have been unsuccessful, as was Manjunath (*loc. cit.*), in attempts to obtain an *N*-methylated indolocarbazole from the bisnitrosamine from *NN′*-dimethyl-*p*-phenylenediamine by reduction with zinc in acetic acid in the presence of *cyclo*hexanone. Plant and Rippon (*J.*, 1928, 1906) reduced the nitrosamine (II; R = NO) in acetic acid containing *cyclo*hexanone and obtained 1-(tetrahydro-9-carbazolyl)*cyclo*pentane-1-carboxylic acid (VI), which decomposed to give tetrahydrocarbazole and *cyclo*pent-1-ene-1-carboxylic acid with hot 60% sulphuric acid, and in other ways. It therefore seemed possible that the bisnitrosamine (III; R = NO, R′ = CN) and the corresponding di*cyclo*hexyl compound might undergo similar conversion into octahydroindolocarbazoles containing 1-cyano*cyclo*alkyl substituents attached to the nitrogen atoms, which would have the advantage over the simpler methyl derivatives that the substituents might be very easily removed from the product. Unfortunately, neither bisnitrosamine could be made to give the substances envisaged.

The difficulty of effecting the above double cyclisation processes suggested the use of aminocarbazoles from which it would be necessary to form only one additional indole system. A convenient compound of this type seemed to be 6-amino-9-methylhexahydrocarbazole (VII) in which the orientation of *p*-phenylenediamine is maintained. This substance was prepared by reduction of the known tetrahydro-9-methyl-6-nitrocarbazole and also, less satisfactorily, from the product of nitrosating hexahydro-9-methylcarbazole. Both nitrogen atoms are basic, and it seemed desirable first to examine similar reactions with the closely related and more easily accessible *p*-aminodimethylaniline. The latter has accordingly been converted into 1-cyano-1-*p*-dimethylaminoanilino*cyclo*pentane, which was hydrolysed *via* the amide to the acid (VIII), but this gave no 3-dimethylaminocarbazole when its sodium salt was fused with sodium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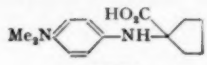
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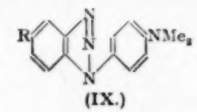
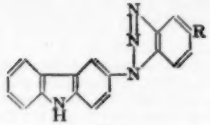

(IX.)

ethoxide and potassium hydroxide. An attempt to apply the Graebe–Ullmann reaction to 1-*p*-dimethylaminophenyl-5-nitrobenzotriazole (IX; R = NO_2) failed, but it is known that the reaction does not proceed well with nitrobenzotriazoles and that better results can be expected when the nitro-group is replaced by acyl or cyano- (see, *e.g.*, Preston, Tucker, and Cameron, *J.*, 1942, 500). The triazoles (IX; R = COMe, COPh, and CN) were accordingly prepared from *p*-aminodimethylaniline, but in no case could the Graebe–Ullmann reaction be successfully applied. This is surprising in view of the fact that the reaction has been used for making amino-, cyano-, and *C*-acyl-carbazoles. The results suggested that 6-aminohexahydro-9-methylcarbazole would be unlikely to give indolocarbazoles in similar reactions, and the use of 3-aminocarbazole in which the ring-nitrogen is non-basic seemed to be more promising. This

has been condensed with 4-chloro-3-nitrobenzonitrile and the product converted through the corresponding amine into 1-3′-carbazolyl-5-cyanobenzotriazole * (X; R = CN) and, when the latter was heated, nitrogen was eliminated with the formation of a cyanoindolocarbazole.



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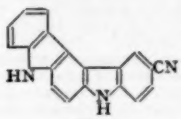

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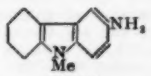

(XII.)

There are two possible structures, but a " linear " arrangement of the rings is less likely on general grounds, and the substance is regarded as 6-cyanoindolo(2′ : 3′-3 : 4)carbazole (XI). It seems probable that other substituted indolo(2′ : 3′-3 : 4)carbazoles could be obtained from 3-aminocarbazole by the Graebe–Ullmann method, but it must be noted that Manjunath (*loc. cit.*) was unable to effect the reaction with the two compounds (X; R = NO_2 and NH_2). In an attempt to carry out a parallel synthesis from 6-amino-1 : 2 : 3 : 4-tetrahydro-9-methylcarbazole (XII), in which the ring-nitrogen is also non-basic, 6-(2-amino-4-cyanoanilino)-1 : 2 : 3 : 4-tetrahydro-9-methylcarbazole has been prepared, but it could not be converted into the requisite triazole.

Experimental.

p-*Di*-(5-*chlorobenzotriazol*-1-*yl*)*benzene* (I; R = Cl).—A mixture of 4-chloro-2-nitroaniline (47 g.), *p*-dibromobenzene (32 g.), and potassium carbonate (39 g.) was heated in nitrobenzene (190 c.c.) containing a little copper powder for 8 hours at 190—200° with mechanical stirring under a short air condenser. The whole was filtered while hot through glass-wool, and, on cooling, NN′-*di*-(4-*chloro*-2-*nitrophenyl*)-p-*phenylenediamine* separated from the solution in red prisms (19 g.). After being refluxed for a short time with ethanol (200 c.c.), it was recrystallised from nitrobenzene, and had m. p. 291—292° (Found: C, 51·7; H, 3·2. $C_{18}H_{12}O_4N_4Cl_2$ requires C, 51·6; H, 2·9%). A solution of sodium (6·5 g.) in ethanol (150 c.c.) was saturated with hydrogen sulphide, the above dinitro-compound (19 g.) added, and the mixture heated until a vigorous reaction set in. After this had subsided, the whole was refluxed for 12 hours, and, when cold, the colourless solid (8·5 g.) was collected, washed with water, and crystallised from xylene, from which NN′-*di*-(2-*amino*-4-*chlorophenyl*)-p-*phenylenediamine* separated in colourless needles, m. p. 202—203° (Found: N, 15·7. $C_{18}H_{16}N_4Cl_2$ requires N, 15·6%). Sodium nitrite (3·4 g.) in a little water was gradually added, with stirring, to the diamine (8·5 g.) in glacial acetic acid (100 c.c.) containing concentrated hydrochloric acid (6·6 c.c.), at 10°. After 2 hours, dilution with water precipitated p-*di*-(5-*chlorobenzotriazol*-1-*yl*)*benzene* (8·3 g.), which crystallised from nitrobenzene in colourless plates, m. p. 325° (decomp.) (Found: C, 56·4; H, 2·7. $C_{18}H_{10}N_6Cl_2$ requires C, 56·7; H, 2·6%).

p-*Di*-(5-*methoxybenzotriazol*-1-*yl*)*benzene* (I; R = OMe).—Prepared from 4-methoxy-2-nitroaniline by methods similar to those described above, NN′-*di*-(4-*methoxy*-2-*nitrophenyl*)-p-*phenylenediamine* (reaction temperature: 185°, for 6 hours) crystallised from nitrobenzene in dark violet needles, m. p. 220° (Found: C, 58·2; H, 4·5. $C_{20}H_{16}O_6N_4$ requires C, 58·5; H, 4·4%), NN′-*di*-(2-*amino*-4-*methoxyphenyl*)-p-*phenylenediamine* from xylene in colourless plates, m. p. 219° (Found: C, 68·5; H, 6·5. $C_{20}H_{22}O_2N_4$ requires C, 68·6; H, 6·3%), and p-*di*-(5-*methoxybenzotriazol*-1-*yl*)*benzene* from nitrobenzene in solvated colourless needles, m. p. 321—323° (Found: N, 20·1. $C_{20}H_{16}O_2N_6,C_6H_5O_2N$ requires N, 19·8%).

p-*Di*-(5-*cyanobenzotriazol*-1-*yl*)*benzene* (I; R = CN).—Powdered anhydrous sodium acetate (4·6 g.) was added to a molten mixture of *p*-phenylenediamine (2 g.) and 4-chloro-3-nitrobenzonitrile (6·1 g.), and the whole heated at 180° with stirring until it solidified. After the mixture had been boiled with ethanol and the residue crystallised from nitrobenzene, NN′-*di*-(4-*cyano*-2-*nitrophenyl*)-p-*phenylenediamine* was obtained in red prisms (3·3 g.), m. p. 317—318° (Found: C, 60·3; H, 3·1. $C_{20}H_{12}O_4N_6$ requires C, 60·0; H, 3·0%). A boiling solution of stannous chloride (20 g.) in concentrated hydrochloric acid (50 c.c.) was added to this substance (2·9 g.) in hot glacial acetic acid (250 c.c.), and the whole boiled for 20 minutes. When cold, the mixture was made alkaline with sodium hydroxide, the solid dissolved in acetic acid (60 c.c.) containing concentrated hydrochloric acid (4 c.c.) at 30°, and the solution treated with aqueous sodium nitrite (1·1 g.). The precipitated p-*di*-(5-*cyanobenzotriazol*-1-*yl*)*benzene* was washed with dilute hydrochloric acid and crystallised from nitrobenzene, from which it separated in colourless prisms, m. p. above 360° (Found: C, 66·2; H, 2·8. $C_{20}H_{10}N_8$ requires C, 66·3; H, 2·8%).

NN′-*Di*-(1-*cyano*cyclo*pentyl*)-p-*phenylenediamine* (III; R = H, R′ = CN).—Potassium cyanide (6·4 g.) in water (20 c.c.) was gradually added to *p*-phenylenediamine (5 g.) and *cyclo*pentanone (7·4 g.) in glacial acetic acid (50 c.c.) at room temperature, and after 24 hours the NN′-*di*-(1-*cyano*cyclo*pentyl*)-p-*phenylenediamine* (9·9 g.), m. p. 149°, which had separated was collected, washed with ethanol, and dried. It crystallised from ethanol in almost colourless needles, m. p. 151—152° (Found: C, 73·2; H, 7·5. $C_{18}H_{22}N_4$ requires C, 73·5; H, 7·5%). Its *bisnitrosamine*, which separated when the diamine was treated

* Ring Index numbering.

with sodium nitrite in acetic acid–hydrochloric acid, crystallised from benzene in pale yellow plates, m. p. 151—152° (decomp.) (Found: C, 61·5; H, 5·8. $C_{18}H_{20}O_2N_6$ requires C, 61·4; H, 5·7%).

NN′-*Di*-(1-*carbamyl*cyclo*pentyl*)-p-*phenylenediamine* (III; R = H, R′ = CO·NH$_2$).—A solution of the above dicyanide (5 g.) in concentrated sulphuric acid (50 c.c.) was kept for 2 days, poured on ice, and made alkaline with ice–concentrated aqueous ammonia. The precipitated NN′-*di*-(1-*carbamyl*cyclo*pentyl*)-p-*phenylenediamine* (4·8 g.) separated from ethanol in colourless plates, m. p. 290—292° (Found: C, 65·6; H, 7·9. $C_{18}H_{26}O_2N_4$ requires C, 65·5; H, 7·9%).

A mixture of the diamide (2·8 g.) and powdered potassium hydroxide (10 g.) was heated at 320° in a copper tube, and the volatile material was condensed and collected. When the distillate was dissolved in dilute acetic acid, the solution shaken with ether, and the aqueous layer shaken for 10 minutes with acetic anhydride (3 c.c.), *NN′*-diacetyl-*p*-phenylenediamine (0·5 g.), identified by mixed m. p. with an authentic specimen, gradually separated. No appreciable amount of insoluble material appeared when the alkali residue was dissolved in water.

NN′-*Di*-(1-*carboxy*cyclo*pentyl*)-p-*phenylenediamine* (III; R = H, R′ = CO$_2$H).—The above diamide (5 g.) was refluxed with concentrated hydrochloric acid (50 c.c.) for an hour, the whole evaporated to dryness on a steam-bath, the residue dissolved in dilute aqueous sodium hydroxide, and the filtered solution acidified with acetic acid. The *NN′*-di-(1-carboxy*cyclo*pentyl)-*p*-phenylenediamine (3 g.), m. p. 253° (decomp.), which separated, could not be satisfactorily recrystallised and was converted into its *diethyl* ester, almost colourless needles, m. p. 101° (from ethanol), by refluxing it with ethanolic hydrogen chloride for 5 hours (Found: C, 68·4; H, 8·0. $C_{22}H_{32}O_4N_2$ requires C, 68·0; H, 8·2%).

When the acid (12 g.) was heated with powdered potassium hydroxide (20 g.) and sodium ethoxide (20 g.) at 300° for an hour in a copper tube, no *p*-phenylenediamine could be detected in the distillate by the above method. After the alkali residue had been treated with water, the dark, insoluble material was dried and distilled under reduced pressure. The substance obtained was crystallised from ethanol in colourless plates, m. p. 250° (Found: C, 79·2; H, 5·5. Calc. for $C_{12}H_{10}N_2$: C, 79·1; H, 5·5%), and was shown to be 3-aminocarbazole by mixed m. p.

3-(1-*Cyano*cyclo*pentylamino*)*carbazole* (IV; R = CN).—Prepared from 3-aminocarbazole by a process similar to that described for *NN′*-di-(1-cyano*cyclo*pentyl)-*p*-phenylenediamine, this *carbazole* crystallised from ethanol in colourless plates, m. p. 138—139° (Found: C, 78·5; H, 6·2. $C_{18}H_{17}N_3$ requires C, 78·5; H, 6·2%). After the cyanide (3 g.) had been refluxed with concentrated hydrochloric acid (70 c.c.) for 5 hours, addition of alkali to the filtered solution precipitated 3-aminocarbazole, which separated from toluene in almost colourless plates (1 g.), m. p. and mixed m. p. 254°.

N′N‴-*Di*cyclo*hexylidene*-p-*phenylenedihydrazine* (V).—*p*-Phenylenedihydrazine dihydrochloride (3·4 g.; Schoutissen, *J. Amer. Chem. Soc.*, 1933, **55**, 4545), *cyclo*hexanone (5 c.c.), and anhydrous sodium acetate (5 g.) were stirred in ethanol (50 c.c.) at 0°, and a mixture of equal volumes of ethanol and water (25 c.c.) was gradually added. After a further 40 minutes' stirring, the yellow solid was collected and quickly dissolved in hot ethanol (60 c.c.), and the filtered solution cooled. The *dihydrazone* was obtained in orange plates (3 g.), m. p. 172° (decomp.) (Found: C, 72·5; H, 8·9. $C_{18}H_{28}N_4$ requires C, 72·5; H, 8·7%), which gradually decomposed on being kept.

NN′-*Dimethyl*-p-*phenylenediamine*.—The following method for the preparation of this substance was found to be more convenient than that described by Willstätter and Pfannenstiel (*Ber.*, 1905, **38**, 2244). Methyl iodide (80 g.) and ethanolic potassium hydroxide (24 g. in 130 c.c.) were added at room temperature to *NN′*-diformyl-*p*-phenylenediamine (33 g.) in ethanol (400 c.c.) and, after being kept overnight, the mixture was heated at 50° for 24 hours. When cold, ethanol was distilled from the filtered solution, and the residue warmed for 2 hours on the steam-bath with concentrated hydrochloric acid (250 c.c.), and made alkaline. After the product had been extracted with ether, and the extract dried (K_2CO_3) and fractionated, *NN′*-dimethyl-*p*-phenylenediamine (15 g.) was collected at 146—148°/16 mm.

NN′-*Di*-(1-*cyano*cyclo*hexyl*)-p-*phenylenediamine*.—Prepared from *cyclo*hexanone by methods similar to those used for the analogous *cyclo*pentyl compounds, *NN′*-di-(1-cyano*cyclo*hexyl)-*p*-phenylenediamine crystallised from ethanol in colourless prisms, m. p. 194° (Found: C, 74·3; H, 8·2. Calc. for $C_{20}H_{26}N_4$: C, 74·5; H, 8·1%), and its *bisnitrosamine* from ethanol in brown prisms, m. p. 171—172° (decomp.) (Found: C, 63·0; H, 6·4. $C_{20}H_{24}O_2N_6$ requires C, 63·2; H, 6·3%). Bucherer and Fischbeck (*J. pr. Chem.*, 1934, **140**, 69) made the dicyanide by a different process, but give the m. p. 169° and no analysis.

6-*Aminohexahydro*-9-*methylcarbazole* (VII).—A mixture of tetrahydro-9-methyl-6-nitrocarbazole (20 g.; Perkin and Plant, *J.*, 1921, **119**, 1825), granulated tin (120 g.), ethanol (200 c.c.), and concentrated hydrochloric acid (200 c.c.) was refluxed for 24 hours, most of the ethanol distilled off, and the residue treated with an excess of aqueous sodium hydroxide. When the product was extracted with ether, the extract dried (K_2CO_3), the solvent removed, and the residue fractionated under reduced pressure, 6-*aminohexahydro*-9-*methylcarbazole* was collected as a pale yellow syrup (10 g.), b. p. 213—215°/16 mm. (Found: C, 77·6; H, 8·9. $C_{13}H_{18}N_2$ requires C, 77·2; H, 8·9%). 6-*Benzamidohexahydro*-9-*methylcarbazole*, obtained from the base by the action of benzoyl chloride and alkali in acetone, separated from ethanol in colourless needles, m. p. 230—231° (Found: C, 78·3; H, 6·9. $C_{20}H_{22}ON_2$ requires C, 78·4; H, 7·2%).

A mixture of the hydrochloride (7 g.) of 6-aminohexahydro-9-methylcarbazole (prepared by passing hydrogen chloride into the base in ether) and 1-chloro-2 : 4-dinitrobenzene (6 g.) in boiling ethanol was treated with a concentrated aqueous solution of sodium carbonate (3·2 g.). After a few minutes the mixture was cooled, and the dark solid was boiled in ethanol with charcoal. 6-(2 : 4-*Dinitroanilino*)-*hexahydro*-9-*methylcarbazole* crystallised from the filtered solution, on cooling, in red prisms (4 g.), m. p. 155—156° (Found: C, 62·2; H, 5·4. $C_{19}H_{20}O_4N_4$ requires C, 62·0; H, 5·4%).

1-p-*Dimethylaminoanilino*cyclo*pentane*-1-*carboxylic Acid* (VIII).—A solution of *p*-aminodimethylaniline (9 g.) and *cyclo*pentanone (6 c.c.) in glacial acetic acid (40 c.c.) was treated at 0° with aqueous potassium cyanide (4·5 g.), and after 4 hours the whole was made alkaline with ice–concentrated ammonia. When the solid was crystallised from aqueous ethanol, 1-p-*dimethylaminoanilino*-1-*cyano*cyclo*pentane* was obtained in colourless needles (8 g.), m. p. 83° (Found: C, 73·2; H, 8·5. $C_{14}H_{19}N_3$ requires C, 73·4; H, 8·3%). It was hydrolysed to the corresponding *amide*, colourless prisms, m. p. 193—194° (from ethanol), in almost theoretical yield by the usual sulphuric acid method (above) (Found: C, 68·4; H, 8·5. $C_{14}H_{21}ON_3$ requires C, 68·0; H, 8·5%). The amide (4 g.) was refluxed for an hour with concentrated hydrochloric acid (50 c.c.), the whole evaporated to a thick paste, the paste shaken with cold dilute aqueous sodium hydroxide, and the filtered solution treated with concentrated aqueous sodium hydroxide. 1-*p*-Dimethylaminoanilino*cyclo*pentane-1-carboxylic acid separated as its sodium salt which (2 g.) was refluxed with methanolic hydrogen chloride for 5 hours. After the methanol had been removed, the residue dissolved in water, and the filtered solution made alkaline, the *methyl* ester, colourless needles, m. p. 69—70° (from water), was precipitated (Found: C, 68·5; H, 8·5. $C_{15}H_{23}O_2N_3$ requires C, 68·7; H, 8·4%).

A mixture of the sodium salt (3 g.), sodium ethoxide (10 g.), and powdered potassium hydroxide (10 g.) was heated at 330° for an hour in a copper tube and, when the distillate was treated with dilute acetic acid and acetic anhydride, *p*-acetamidodimethylaniline (0·4 g.), m. p. and mixed m. p. 129—130°, was obtained. No 3-dimethylaminocarbazole was isolated from the material obtained by treating the alkali residue with water.

1-p-*Dimethylaminophenyl*-5-*nitrobenzotriazole* (IX; R = NO_2).—A boiling aqueous solution of hydrated sodium sulphide (9·3 g.) was added to 4′-dimethylamino-2 : 4-dinitrodiphenylamine (6·2 g.; Lellmann and Mack, *Ber.*, 1890, **23**, 2739) in hot ethanol (45 c.c.), and after the vigorous reaction had subsided the whole was boiled for 10 minutes, filtered whilst hot, and treated with water (100 c.c.). When the mixture was again boiled and allowed to cool, 2-*amino*-4′-*dimethylamino*-4-*nitrodiphenylamine*, golden-yellow prisms (5 g.), m. p. 185° (from ethanol), separated (Found: C, 61·9; H, 6·2. $C_{14}H_{16}O_2N_4$ requires C, 61·8; H, 5·9%). Sodium nitrite (1 g. in concentrated aqueous solution) was added to the amine (3·5 g.) in glacial acetic acid (20 c.c.), containing a molecular proportion of hydrochloric acid, at 5°. After the addition of more acetic acid (20 c.c.), the whole was warmed to 100°, allowed to cool, and the solid crystallised from ethanol, from which 1-p-*dimethylaminophenyl*-5-*nitrobenzotriazole* separated in yellow plates (2·8 g.), m. p. 231—232° (Found: C, 59·2; H, 4·9. $C_{14}H_{12}O_2N_5$ requires C, 59·4; H, 4·6%).

5-*Acetyl*-1-p-*dimethylaminophenylbenzotriazole* (IX; R = Ac).—Sodium carbonate (3 g. in concentrated aqueous solution) was gradually added to *p*-aminodimethylaniline dihydrochloride (4 g.) and 4-bromo-3-nitroacetophenone (4 g.) in boiling ethanol (40 c.c.), and the whole refluxed for ½ hour (compare Lellmann and Mack, *loc. cit.*). When the product (3·6 g.) which separated on cooling was recrystallised from ethanol, 4-*acetyl*-4′-*dimethylamino*-2-*nitrodiphenylamine* was obtained in chocolate coloured plates, m. p. 145—146° (Found: C, 64·5; H, 5·9. $C_{16}H_{17}O_3N_3$ requires C, 64·2; H, 5·7%). Stannous chloride (15 g.) in concentrated hydrochloric acid (40 c.c.) was added to the nitro-compound (3·2 g.) in hot glacial acetic acid (50 c.c.), and the whole boiled for a few minutes, cooled, and made alkaline with aqueous sodium hydroxide. After the solid had been crystallised from ethanol, 4-*acetyl*-2-*amino*-4′-*dimethylaminodiphenylamine* was isolated in yellow prisms (1·9 g.), m. p. 155—156° (Found: N, 15·5. $C_{16}H_{19}ON_3$ requires N, 15·6%). The amine (1·1 g.) in glacial acetic acid (20 c.c.) containing concentrated hydrochloric acid (2 c.c.) was treated at 5° with a slight excess of aqueous sodium nitrite, and, after 2 hours, the whole was made alkaline with ammonia. The precipitated 5-*acetyl*-1-p-*dimethylaminophenylbenzotriazole* crystallised from ethanol in yellow needles, m. p. 153—154° (Found: N, 20·2. $C_{16}H_{16}ON_4$ requires N, 20·0%). When the compound was purified by adsorption on alumina and then crystallised from toluene, a polymorphic form was obtained as pale yellow needles, m. p. 182—183° (Found: N, 20·2%). This seems to be an example of the stabilisation of the lower-melting form by a trace of impurity, observed for other compounds by Gorvin (*J.*, 1950, 407).

5-*Benzoyl*-1-p-*dimethylaminophenylbenzotriazole* (IX; R = COPh).—Prepared from 4-chloro-3-nitrobenzophenone like the analogous compounds from 4-bromo-3-nitroacetophenone, 4-*benzoyl*-4′-*dimethylamino*-2-*nitrodiphenylamine* crystallised from methanol in dark red needles, m. p. 159—161° (Found: C, 69·9; H, 5·4. $C_{21}H_{19}O_3N_3$ requires C, 69·8; H, 5·3%), 2-*amino*-4-*benzoyl*-4′-*dimethylaminodiphenylamine* from ethanol in yellow prisms, m. p. 208—210° (Found: N, 12·4. $C_{21}H_{21}ON_3$ requires N, 12·7%), and 5-*benzoyl*-1-p-*dimethylaminophenylbenzotriazole* from ethanol, after purification by adsorption on alumina, in pale yellow needles, m. p. 162—164° (Found: N, 16·2. $C_{21}H_{18}ON_4$ requires N, 16·4%).

5-*Cyano*-1-p-*dimethylaminophenylbenzotriazole* (IX; R = CN).—Prepared from 4-chloro-3-nitrobenzonitrile like the related compounds from 4-bromo-3-nitroacetophenone, 4-*cyano*-4′-*dimethylamino*-2-*nitrodiphenylamine* separated from ethanol in dark red plates, m. p. 156—157° (Found: C, 64·1; H, 5·2. $C_{15}H_{14}O_2N_4$ requires C, 63·8; H, 5·0%), 2-*amino*-4-*cyano*-4′-*dimethylaminodiphenylamine* from methanol in pale yellow prisms, m. p. 133—134° (Found: N, 22·2. $C_{15}H_{16}N_4$ requires N, 22·2%), and 5-*cyano*-1-p-*dimethylaminophenylbenzotriazole* from methanol in yellow needles, m. p. 218—220° (Found: N, 26·9. $C_{15}H_{13}N_5$ requires N, 26·6%).

6-*Cyanoindolo*(2′ : 3′-3 : 4)*carbazole* (XI).—After 3-aminocarbazole (8 g.), 4-chloro-3-nitrobenzonitrile (8 g.), and anhydrous sodium acetate (9 g.) had been refluxed for 6 hours in ethanol (300 c.c.), 3-(4-*cyano*-2-*nitroanilino*)*carbazole* separated on cooling, and, when recrystallised from acetic acid, it was obtained in red-brown prisms (9·5 g.), m. p. 190—191° (Found: C, 69·5; H, 3·9. $C_{19}H_{13}O_2N_4$ requires C, 69·5; H, 3·7%). The nitro-compound (9·5 g.) was reduced with stannous chloride as described above for similar substances, and 3-(2-*amino*-4-*cyanoanilino*)*carbazole* was isolated from amyl alcohol in colourless plates (4·3 g.), m. p. 267—269° (Found: N, 18·3. $C_{19}H_{14}N_4$ requires N, 18·8%). A solution of the amine (4 g.) in glacial acetic acid (90 c.c.) and concentrated hydrochloric acid (7 c.c.) was treated with

the theoretical amount of sodium nitrite (0·93 g.) in water. Use of an excess of the reagent led to further reaction with formation of material difficult to remove from the product. *1-3′-Carbazolyl-5-cyanobenzotriazole* (X; R = CN) crystallised from acetic acid in colourless plates (2 g.), m. p. 279—280° (Found: N, 22·7. $C_{19}H_{11}N_5$ requires N, 22·7%). The triazole (1 g.) was heated at 360° until evolution of nitrogen ceased, the residue extracted with boiling ethanol (charcoal), and the filtered solution diluted with water. When the precipitate was crystallised from aqueous ethanol, *6-cyanoindolo(2′:3′-3:4)-carbazole* was obtained in pale brown prisms (0·2 g.), m. p. 310—312° (Found: C, 80·7; H, 4·1; N, 14·5. $C_{19}H_{11}N_3$ requires C, 81·1; H, 3·9; N, 14·9%). It dissolved in cold concentrated sulphuric acid to give a green solution, and it exhibited a blue fluorescence in ethanol.

6-(2-*Amino*-4-*cyanoanilino*)*tetrahydro*-9-*methylcarbazole*.—The following method was found to be more convenient than that described by Perkin and Plant (*loc. cit.*) for the preparation of 6-amino-tetrahydro-9-methylcarbazole. Molten hydrated sodium sulphide (80 g.) was poured slowly into a suspension of tetrahydro-9-methyl-6-nitrocarbazole (10 g.) in hot ethanol (100 c.c.), the whole refluxed for 5 hours, most of the ethanol distilled off, and the residue diluted with water. When the precipitate was crystallised from aqueous ethanol, the amine was obtained in colourless needles (5 g.), m. p. 105—106°. After a mixture of the amine (4·8 g.), 4-chloro-3-nitrobenzonitrile (4·3 g.), and anhydrous sodium acetate (2 g.) in ethanol (75 c.c.) had been heated on the steam-bath for ½ hour and allowed to cool, the dark red 6-(4-*cyano*-2-*nitroanilino*)*tetrahydro*-9-*methylcarbazole* (6 g.) which separated was recrystallised from benzene and obtained in red prisms, m. p. 197—198° (Found: C, 69·6; H, 5·2. $C_{20}H_{18}O_2N_4$ requires C, 69·4; H, 5·2%). When reduced with stannous chloride as described above for related nitro-compounds, it gave 6-(2-*amino*-4-*cyanoanilino*)*tetrahydro*-9-*methylcarbazole*, almost colourless prisms, m. p. 220—221° (from xylene) (Found: N, 17·5. $C_{20}H_{20}N_4$ requires N, 17·7%).

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DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, October 11th*, 1950.]

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101. *Analysis of Inorganic Compounds by Paper Chromatography. Part I. Movement of Cations with Complex-forming Solvent Mixtures.*

By F. H. POLLARD, J. F. W. MCOMIE, and I. I. M. ELBEIH.

The behaviour of the 24 cations of the ordinary qualitative tables with a number of different solvent mixtures, alone and with complex-forming reagents has been investigated. Three solvent mixtures, butanol–water containing benzoylacetone, collidine–water, and dioxan containing antipyrine, are suggested for the general scheme of qualitative analysis, details of which are given in Part II (following paper). The existence of new complexes of cations with collidine is reported as a preliminary to further investigation.

RECENT developments of paper chromatography have opened up new possibilities for qualitative and quantitative separations of cations and anions. In an earlier communication (*Faraday Soc. Discussions*, No. 7, 1949, p. 183) the possibility was suggested of a new scheme of qualitative analysis using paper chromatography only. For such a purpose, the traditional division of cations into groups has been abandoned, and the analysis depends solely on the different chromatograms obtained with suitable solvent mixtures.

One of the main factors in paper chromatography of inorganic compounds is the distribution between an organic solvent and water. Other workers have shown (cf. Linstead *et al.*, *J.*, 1950, 516 for a complete list of references) that the chlorides, nitrates, and acetates of certain cations are sufficiently soluble in organic solvents to enable movement to take place, but our investigations show that it is often preferable to convert the original salt on the paper into a complex such as that with benzoylacetone.

We have investigated a large number of solvents and organic reagents capable of forming complexes with cations, and have shown that the movement of many cations depends, not only on the complex formed, but also on the solubility of that complex in the organic solvent. The movements of 24 individual cations in the best solvent mixtures are shown in Table I, while details of other eluting mixtures which have special value for certain groups of cations are described in the Experimental section of Part II. Our analyses, described in Part II, are based on three solvent mixtures: butanol–water containing benzoylacetone, collidine–water, and dioxan containing antipyrine.

For the movement of cations there are a number of variable factors, *viz.*, solvent mixture, complexing agent, pH, temperature, nature and state of the paper support; and for the

separation of several cations, the possibility of displacement. Until the relative importance of such factors is known, the work must remain empirical and be guided by general principles for the prediction of the movement and separation of cations.

A general spraying reagent for the detection of the majority of cations has already been discussed (see Pollard *et al.*, *loc. cit.*) and consists of a mixture of kojic acid and 8-hydroxyquinoline which reveals the position of cations under ultra-violet light as either fluorescent or dark spots. The sensitivity of detecting reagents is of importance since it partly determines the minimum quantity of any cation which can be chromatographed and detected. The fluorescent reagent is much more sensitive than ammoniacal hydrogen sulphide, which is itself valuable for detecting those cations which form coloured sulphides. Some comparative figures for the sensitivity of these reagents with stationary spots are quoted in Table II, but allowance must be made for diffusion into a larger area when estimating the minimum quantity which can be detected on the chromatogram.

TABLE I.

Movements of cations with different solvent mixtures.

R_F values.

	Butanol containing:					Dioxan containing		
	dibenzoylmethane.	benzoylacetone.	acetylacetone.	acetoacetic ester.	antipyrine.	antipyrine.	Collidine.	Pyridine.
Ag	0·18	0·10	0·15	0·18	0·19	0·08	0·78	0·88
Hg^{+}	0·23	0·24	0·43	0·50	0	0·43	0	0·86
Pb	0·11	0·03	0·09	0·09	0·10	0·15	0	—
Hg^{2+} ...	0·23	0·31	0·43	0·50	0	0·42	0	0·86
Bi	0·15	0·02	0·23	0·20	0·20	0·63	0	0
Cu	0·13	0·22	0·12	0·15	0·17	0·24	0·76	0·85
Cd	0·13	0·05	0·12	0·15	0·13	0·18	0·76	0·87
As	0·42	0·43	0·43	0·45	0·50	0·18	0·65	0·75
Sb	0	0	0·02	0	0	0·65	0·38	0·72
Sn^{2+}	0·73	0·58	0·82	0·70	0·73	0·77	0	0
Sn^{4+}	0·65	0·55	0·81	0·65	0·68	0·58	0	0
Al	0·13	0·03	0·09	0·10	0·09	0·03	0	0
Cr	0·13	0·03	0·09	0·10	0·09	0·01	0	0
Fe^{3+}	0·20	0·95	0·43	0·13	0·14	0·10	0	0
Zn	0·14	0·05	0·10	0·12	0·10	0·08	0·75	0·86
Mn	0·16	0·07	0·11	0·13	0·12	0·09	0·71	0·87
Co	0·13	0·06	0·10	0·12	0·11	0·05	0·74	0·88
Ni	0·13	0·03	0·09	0·12	0·09	0·05	0·76	0·87
Ca	0·11	0·05	0·08	0·12	0·09	0·10	0·52	—
Sr	0·08	0·04	0·07	0·08	0·05	0·04	0·40	—
Ba	0·06	0·02	0·09	0·06	0·04	0·02	0·26	—
Mg	0·11	0·06	0·10	0·13	0·10	0·04	0·65	0·85
K	0·10	0·05	0·10	0·11	0·06	0·03	0·32	—
Na	0·10	0·06	0·10	0·11	0·06	0·04	0·42	—

TABLE II.

Comparison of the sensitivity (in μg.) of hydrogen sulphide and fluorescent spray.

Cation:	Pb.	Cu.	Cd.	Al.	Fe.	Zn.	Co.	Mn.	Ca.	Mg.	K.	Na.
H_2S	0·3	0·5	2·5	—	0·03	—	0·03	—	—	—	—	—
Fluorescent spray ...	0·05	0·03	0·05	0·03	0·03	0·1	0·03	0·03	2·5	0·03	5	5

When the paper is sprayed with our fluorescent mixture and viewed under ultra-violet light, the position of the two liquid fronts (Linstead, *loc. cit.*) is clearly visible. The acid portion is a non-fluorescent region some distance behind the main liquid front, and the space between the acid front and the main liquid front is brightly fluorescent. If the paper is afterwards treated with ammonia, the acid region becomes fluorescent too. At low acidities (*i.e.*, mixtures prepared with 0·1N-acid) the acid front reaches to an $R_F = 0·5$, but at higher acidities (*i.e.*, with 3N-acid) the acid front ($R_F = 0·9$) almost coincides with the main front. It would seem, therefore, that the pH of the solvent mixture will vary as the liquid moves down the paper, and hence the R_F values of cations may vary with the distance moved.

EXPERIMENTAL.

Procedure.—The apparatus, procedure, and preparation of solvent mixtures and cationic solutions have been described in our earlier communication (*loc. cit.*). Tests have been made under the conditions recommended by other workers (Linstead, *loc. cit.*; Longenecker, *Anal. Chem.*, 1949, **21**, 1402),

different widths of filter paper (from ½" upwards) and different types of string being used. We favour, however, a width of paper (about 4 cm. for each cation) which allows the chromatogram to form without interference from the edges of the paper. Provided that adequate precautions are taken to keep the paper strip reasonably taut, the upward movement of the solvent mixture can yield quite as good a chromatogram as the downward movement.

Results.—(I) *The effect of the anion on the movement of the cation.* When the copper salts of the following anions were eluted with a mixture of butanol, water, and acetic acid (5 : 4 : 1), the ions moved in the order indicated: citrate, tartrate and sulphate ($R_F = 0$), chloride ($R_F = 0{\cdot}08$), nitrate ($R_F = 0{\cdot}12$), benzoylacetone complex ($R_F = 0{\cdot}20$), acetylacetone complex ($R_F = 0{\cdot}20$), and acetate ($R_F = 0{\cdot}27$). The quality of the spots was best with benzoylacetone. Addition of 10% of saponin and 5% of glycerol to the solvent mixture improved the definition in the case of the acetate.

It would clearly be inconvenient, even if possible, to begin with complexes such as those with benzoylacetone, and the choice had to be made between the acetate, nitrate, and chloride as the original salt. As is well known, the acetates of many cations show a great tendency to hydrolyse, whilst some chlorides are insoluble. Consequently, we have usually begun with the nitrates and aimed to produce the complexes *in situ* by adding a complex-forming reagent to the solvent mixture.

(II) *The movement of cations in different solvent mixtures.* A very wide range of solvents, with and without the addition of complex-forming reagents, and in the presence of different amounts of acid (or alkali) to produce the right pH, have been tried. Most of the later work has been done with nitrates as the starting material, though initially we used acetates (*Nature*, 1949, **163**, 292). Where it was not convenient to use nitrates, other salts, *e.g.*, the chlorides of Sn^{2+}, Sn^{4+}, and Cr^{3+}, the tartrate of antimony, and an aqueous solution of arsenious oxide, were employed. In all cases the solutions contained sufficient acid to prevent hydrolysis, but it was found inadvisable to have more acid present than was just necessary for this purpose.

Too large amounts of cation tended to overload the paper and to produce chromatographic spots with tails; for example, with copper the best results were obtained by using 0·02 c.c. of 0·1N-copper nitrate, larger amounts of copper producing tailing. In general, the optimum quantity of material to use was 0·02 c.c. of 0·1N-solutions of Ag^+, Hg^+, Hg^{2+}, Pb^{2+}, Bi^{3+}, Cu^{2+}, Cd^{2+}, Al^{3+}, Fe^{3+}, Zn^{2+}, Mn^{2+}, Co^{2+}, Ni^{2+}, As^{3+}, Sb^{3+}, and 0·02 c.c. of 0·2N-solutions of Ca^{2+}, Sr^{2+}, Ba^{2+}, Mg^{2+}, K^+, Na^+, Sn^{2+}, Sn^{4+}, Cr^{3+}. Much smaller quantities than these are within the limits of detection.

Solvent Mixtures.—(1) *Butanol and water, with different complex-forming reagents.* (a) With nitric acid. The effect of nitric acid has been previously described (Pollard *et al.*, *Faraday Soc. Discussions*, 1949, No. 7, p. 183).

(b) With acetoacetic ester. When using 1 : 1 mixtures prepared with butanol and water or dilute nitric acid (0·1N- to 3N-nitric acid containing 5% of acetoacetic ester), the best separations and most symmetrical spots were obtained with mixtures prepared with N-nitric acid. At lower acidities there was pronounced tailing, which again became the disturbing factor at higher acidities.

(c) With acetylacetone. The best mixture was found to be butanol–2N-nitric acid (1 : 1) and 1% acetylacetone for the general movements, though Cu^{2+} and Cd^{2+} separated when 0·1N-acid was used but did not do so at higher acidities; there was serious forward tailing only with Hg^+, Hg^{2+}, Al^{3+}, and Fe^{3+}. An interesting point is that the tailing produced with iron gradually became more and more pronounced with increasing acidity, and with the mixture using 1N-nitric acid two distinct spots were obtained; the upper one in the acid zone was deep violet (probably ferric complex), the lower one beyond the acid front being orange-yellow (probably ferrous–acetylacetone complex).

(d) With benzoylacetone. The best mixture was found to be butanol–0·1N-nitric acid (1 : 1) and 0·5% benzoylacetone, and since this is the mixture which we use for one of our solvents in our later separations, we have quoted in detail our observations on the effect of changing the acidity of the acid. Table III illustrates the general trend of the effect of varying acidity on the movement when complex-forming reagents are used, which is undoubtedly associated with the stability of the respective complexes at different pH's. The separation of iron into two spots was further investigated by using initial solutions of iron of varying acidity and the mixture quoted above. It was found that with the stronger initial acid solutions the two spots appeared again, and qualitative tests indicated that the one with R_F 0·6 was a ferric, and the other, of R_F 0·95, was a ferrous compound. This illustrates the reducing effect of the cellulose and the change in relative stability of the ferric and ferrous benzoylacetone complexes as the pH changes.

TABLE III.

Solvent mixture.	Observations.
Butanol–water (1 : 1) and 0·5% benzoylacetone	Forward tailing with Hg^+, Hg^{2+}, Sn^{2+}, Sn^{4+}, Al^{3+}, Cr^{3+}, Zn^{2+}, Co^{2+}, Ni^{2+}. One spot for Fe^{3+} (R_F 0·95) with long tailing. Cu^{2+} and Cd^{2+} separate in spite of forward tailing of Cu^{2+}.
As above, but water replaced by 0·05N-aqueous HNO_3	Forward tailing with Cu^{2+} and Al^{3+} only. Tailing of Fe^{3+} decreases. Cu^{2+} and Cd^{2+} still move to different positions.
Ditto, with 0·1N-HNO_3	Best spots and best movements of cations. Fe forms one spot.
Ditto, with 0·2 or 0·3N-HNO_3	Less difference in movements of Cu^{2+} and Cd^{2+}. Long tails with Hg^+ and Hg^{2+}. Fe^{3+} forms two spots, R_F 0·6 and 0·95.
Ditto, with 0·4 or 0·5N-HNO_3	No difference in movement of Cu^{2+} and Cd^{2+}. The lower spot of the Fe^{3+} is smaller. Hg^+ and Hg^{2+} washed down to solvent front with long tails.
Ditto, with 1·0, 1·5, 2, 2·5, or 3N-HNO_3	Cu^{2+} and Cd^{2+} move to the same extent. Tailing forward of Sb^{3+}. Long tails with Hg^+ and Hg^{2+}. One spot for Fe^{3+}, R_F 0·6.

In order to establish that the various complexes were formed during the passage of the solvent, a trial was made on a cellulose column to separate Fe, As, Cu, and Cd, the solvent mixture fractions containing the respective cations being collected and evaporated. The crystals of the iron and the copper compound thus obtained both had m. p.s corresponding to their benzoylacetone complexes, namely, 224° and 195°, respectively, while cadmium did not yield crystals of the benzoylacetone complex, and arsenic on evaporation gave a white precipitate which sublimed at 193° and was probably arsenious oxide. Thus, as would be expected, not all the cations move as their benzoylacetone complexes.

(e) With dibenzoylmethane. The best mixture was butanol–2N-nitric acid (1 : 1) and 0·1% dibenzoylmethane, and this gave the best spots obtained with Hg^{+}, Hg^{2+}, Sn^{2+}, and Fe^{3+}; the only other useful feature is that the separation for Cu^{2+} and Cd^{2+} is quite good when *only water* is used to prepare the solvent mixture.

(f) With dimethylglyoxime. This was not found to be so good for the purpose in view. There was hardly any movement of cations unless the acidity was fairly high, and at very high acidity most of the spots had long tails. The best mixture was butanol–N-nitric acid (1 : 1) and 0·1% dimethylglyoxime, which gave reasonable results with Hg^{+}, Hg^{2+}, and Sb^{3+}.

(g) With antipyrine. A mixture of butanol and N-nitric acid (50 : 50) containing 1% of antipyrine produced movements of some cations, *e.g.*, Ag^{+}, Pb^{2+}, Bi^{3+}, Cu^{2+}, Cd^{2+}, As^{3+}, and Sn, without tailing, but on the whole the movements and separations were not as good as those for antipyrine in dioxan.

(h) With other complexing reagents. Catechol, protocatechuic acid, 8-hydroxyquinoline, and ammonium thiocyanate could not be used with nitric acid, since they readily oxidised and were generally not satisfactory.

The addition of pyridine or collidine as complexing reagents produced no valuable results, except that butanol, 0·1N-nitric acid, and collidine (5 : 4 : 1) produced the only separation of Cd (R_F 0·24) and Zn (R_F 0·06). Usually there was movement accompanied by pronounced tailing.

(2) *Collidine mixtures.* The collidine–water mixture is heterogeneous at room temperature. Mixtures with 50% of 0·1, 0·2, 0·3, and 0·4N-nitric acid cause a rise in temperature, but those with 0·6N-nitric acid raise the temperature and also lead to the formation of a homogeneous mixture which does not separate into two layers on cooling, as the others do. With these mixtures very good separations of many cations were obtained and are recorded for the best mixture (collidine and 0·4N-nitric acid, 1 : 1) in Table I. The observations on the effect of acidity are quoted in Table IV.

TABLE IV.

Solvent mixture.	Observations.
Collidine with water or 0·1N-HNO_3 (1 : 1)	Tailing in Cu^{2+}, Cd^{2+}, Sb^{3+}, Zn^{2+}, Mn^{2+}, Co^{2+}, Ni^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}, Mg^{2+}, K^{+}, Na^{+}.
Ditto, with 0·2 or 0·3N-HNO_3	Tailing is less for Cu^{2+}, Sb^{3+}, Zn^{2+}, Mn^{2+}, and Co^{2+}. Gradual concentration of spots for most cations.
Ditto, with 0·4N-HNO_3	Best spots with almost no tailing at all.
Ditto, with 0·5N-HNO_3	Tailing forwards with Hg^{+}, Hg^{2+}, Cu^{2+} and Co^{2+}.
Ditto, with 0·6N-HNO_3 (see above)	Washing down of most of the cations to the solvent front or excessive tailing.

A series of qualitative test-tube experiments with the 24 cations and collidine shows that only the cations which move in the collidine mixture form complexes with collidine that are soluble in that solvent. Only one collidine complex, the azide $(C_7H_9N)_2Cu(N_3)_2$, has been recorded (Cirulis and Straumanis, *J. pr. Chem.*, 1943, **162**, 307). The formation and properties of these complexes are being further investigated.

(3) *Pyridine mixtures.* Pyridine, like dioxan, is completely miscible with water, so only one layer was formed when it was mixed with different quantities of water or acid. The best mixture consisted of 60% of pyridine and 40% of water, and this gave movement with all cations except Pb, Ca, Sr, Ba, K, and Na where, if there was movement, it was accompanied by considerable tailing.

Pyridine, alone or with from 1 to 6% of concentrated nitric acid, either gave considerable forward tailing or washed the cations to the solvent front. Somewhat similar results were obtained with mixtures of 90% and 10% of water or different concentrations of dilute nitric acid (from 0·5 to 2N.), but in this case two spots appeared for Hg^{+}, Hg^{2+}, and Cd^{2+}. Pyridine with 2% or 4% of ammonium thiocyanate added gave movement with Ca, Sr, Ba, K, and Na, accompanied by much tailing, whereas other spots were either washed down or did not move at all.

The R_F values for Pb, Ca, Sr, Ba, K, and Na were unsatisfactory owing to tailing. The quality of the spots with pyridine was not as good as those with collidine.

(4) *Dioxan mixtures.* Dioxan, which is miscible with water, was not satisfactory when used alone, but a mixture of 100 c.c. of *pure* dioxan, 1 g. of antipyrine, 1 c.c. of concentrated nitric acid, and 2·5 c.c. of water was found to move a number of cations with good separation and concentrated spots. The R_F values are recorded in Table I, and this solvent mixture is the third one used in our scheme. For some cations, *e.g.*, Al and Sb, the R_F value varies with the initial concentration of the cation.

(III) *The effect of the filter-paper on the movement of the cations.* (a) Different types of filter-paper. Other workers, particularly Hanes and Isherwood (*Nature*, 1949, **164**, 1107), when separating phosphoric esters, have stated that the type and purity of the paper will determine the concentration of the spots and the movement of the compounds. Experiments with Whatman No. 1, No. 54, No. 541 for chromatography, and purified No. 1 (*i.e.*, treatment with 8-hydroxyquinoline in aqueous alcohol, followed by thorough washing in aqueous alcohol and drying), using the usual cation solutions and the butanol–

water–benzoylacetone mixture showed that: (i) There was no general improvement in the concentration of spots and the movement was the same for all filter-papers. (ii) The purified No. 1 had no "ghost" spots remaining on the starting line, although they are present in very faint shadows with No. 54 and No. 541—slightly less than with No. 1. (iii) The only marked improvement we were able to observe was that the solvent mixture ran more quickly over No. 54, and there was slightly less tendency for tailing of the spots.

(b) Treatment of the filter-paper. Attempts were made to change the condition of the paper by: (i) Oxidising it with sodium periodate and bromine water to convert some of the CH_2·OH groups of the cellulose into CO_2H groups; papers so treated exhibited increasing tendency to stop movement of the cations and produced excessive tailing where movement did occur. (ii) Treatment with nitric acid: (*a*) Papers soaked in different concentrations of dilute nitric acid (5—20%) for ½ hour, washed, and dried, gave slightly better movements, but tailing was not completely prevented. (*b*) Papers soaked in mixtures of nitric and sulphuric acids (5% H_2SO_4 and 10% HNO_3; or 7% H_2SO_4 and 14% HNO_3) for 10 hours, then washed with distilled water and dried, led to the stopping of the movement of most of the spots, though there was a slight tailing forward. (iii) Treatment with succinic anhydride to increase the number of CO_2H groups present on the paper also led to an increasing tendency for the cations not to move, or to a slight tailing forward.

Our conclusion from these experiments was that for ordinary analytical work there were no great advantages to be gained in any treatment of the paper which we have tried.

In some early experiments we soaked Whatman No. 1 paper in methyl alcohol for several hours to lessen the water content of the paper, and then tried to chromatograph the cations with a butanol–glacial acetic acid (9 : 1) mixture. In this case there was hardly any movement of the cations, but with untreated Whatman No. 1 and water only as the solvent, all the cations were washed down to the solvent front with long tailings. When a mixture of butanol, water, and acetic acid (5 : 5 : 1) was employed as the solvent mixture, the cations moved. This indicates that water has an important function in this type of separation.

(IV) *Effect of temperature on the separations, spots, and solvent mixtures.* The overall effect of temperature was investigated by using the three general solvent mixtures based on butanol, collidine, and dioxan mentioned earlier, and placing the whole tank in a temperature-controlled air cupboard at 16°, 25°, or 38°. In general, the positions to which the cations move do not seem to change with temperature, but the increased rate of flow of the solvent mixtures enables quicker separations to be achieved especially at 25°. At too high a temperature (*i.e.*, 38°) there is considerable transverse diffusion of the spots and excessive tailing. With a fairly volatile solvent like dioxan, the increased evaporation of the solvent from the paper, if the tank is not completely saturated with vapour, has the effect of slowing the movement. It is therefore not easy to determine the real effect for dioxan.

Further investigation of the temperature effects will be carried out later.

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102. *The Analysis of Inorganic Compounds by Paper Chromatography. Part II. Analysis of Cations and Anions.*

By F. H. POLLARD, J. F. W. MCOMIE, and I. I. M. ELBEIH.

The application is reported of three solvent mixtures, (A) butanol–water containing benzoylacetone, (B) collidine–water, and (C) dioxan containing antipyrine, to the general qualitative analysis of the 24 cations of the ordinary analysis tables. A large number of mixtures of cations have been chromatographed without being first separated into groups. Various techniques have been used, namely, one-way chromatograms using one, two, or three solvents, either separately or in combination, or two-way chromatograms, using two or three solvents in combination. The methods have been tried with unknown mixtures.

Suitable solvent mixtures for the separation of Cd and Zn; Th and U; K, Ti, V, Mo, and Fe are reported. The separation of Mo from those elements usually associated with it in agricultural analyses is described.

The R_F values for the movement of anions in a solvent mixture, butanol–pyridine–ammonia, are recorded for chloride, bromide, iodide, chlorate, bromate, iodate, nitrite, nitrate, arsenite, arsenate, carbonate, phosphate, chromate, thiocyanate, and sulphate. The separation of certain groups of these anions is reported. The independent movement of anion and cation is noted.

QUALITATIVE analysis based entirely upon filter-paper chromatography, without any previous chemical separation into groups, has been found to be practicable. By using the three solvent mixtures specified above, either singly or together in one-way or two-way processes, a very large

number of cationic mixtures containing up to seven or more cations can be analysed. The actual procedure adopted will depend on the mixture to be analysed and the quantity available.

The predictions made from the study of single cations described in Part I (preceding paper) are found to hold for most of the cations when mixed. There are a few instances where interference, which might be classed as displacement, occurs when certain cations are together, *e.g.*, As, Sb, and Sn, or when a very large excess of one salt is present, *e.g.*, $NaNO_3$ with smaller quantities of other cations. Sometimes this slight displacement tends to improve the separation. Even when the cations do not move exactly according to the R_F values for the single cation (see Table I, Part I), there is no serious difficulty about identification, since quite characteristic tests can be applied and the position of most cations can be revealed by the fluorescent spray or ammoniacal hydrogen sulphide (see Pollard *et al.*, *Faraday Soc. Discussions*, No. 7, 1949, p. 186).

The anions originally associated with the cations in the mixture do not seem to be very important since, with the solvent mixtures used, the cations are usually converted on the paper into soluble complexes. Some abnormalities have been observed when phosphates, tartrates, arsenates, or large quantities of ammonium salts are present, but these have not yet been fully studied.

From a study of the movement of single anions described in the Experimental section, we have been able to predict and achieve the separation of a number of mixtures of anions, and also show that the anion associated with the cation does not always move to the same position on the paper as the cation, especially when the latter is Na^+ or K^+. Clearly, this depends on the ionic or covalent nature of the compound.

Experimental.

Apparatus.—Several types of apparatus have been used according to the width of filter-paper (Whatman No. 1) required for the separation, but, in general, the arrangement is exactly similar to that already in use for chromatography of organic compounds. The minimum width of paper for the analysis of a single spot by a one-way procedure was 4 cm., and sheets 27 cm. square were suitable for the two-way method. Thus, glass vessels ranging from 200-c.c. cylinders to tanks, 10 × 13 × 16 in., are used containing a suitably supported glass trough, to hold the organic solvent mixture. Great care is taken to make sure that the vessels are air-tight during an experiment, and variations in temperature are avoided by placing the apparatus in an insulated cupboard.

Preparation of Solvents.—(a) *Butanol mixture.* The benzoylacetone (5 g.) is first dissolved in *n*-butanol (50 c.c.), and then shaken with 0·1N-nitric acid (50 ml.). When equilibrium is attained, the upper layer is placed in the trough, and the aqueous layer put at the bottom of the tank to keep the atmosphere within saturated with vapour.

(b) *Collidine mixture.* 2 : 4 : 6-Collidine is shaken with an equal volume of 0·4N-nitric acid, and when the mixture separates on cooling, the collidine and the aqueous layer are used as above.

(c) *Dioxan mixture.* Antipyrine (1 g.) is dissolved in a mixture of pure dioxan (100 c.c.), concentrated nitric acid (1 c.c.), and water (2·8 c.c.), and this mixture is used in the trough, since no aqueous layer separates, the above forming a homogeneous mixture.

Preparation of Known Mixtures.—Equal volumes of the solution of individual cations (Pollard *et al.*, *loc. cit.*) are mixed according to the mixture of cations required for investigation. Care is taken not to use mixtures which are likely to lead to the precipitation of any of the cations.

Preparation of Unknown Mixtures.—A 2% solution of the unknown mixture is prepared either by dissolving the solid in (i) distilled water and then slightly acidifying it with one or two drops of 2N-nitric acid, or (ii) a few c.c. of 2N-nitric acid or 50% nitric acid and diluting the product to the necessary concentration with distilled water. The pH should be adjusted to about 1. If the unknown mixture will not completely dissolve in the above solvents, then the insoluble portion can be removed by centrifuging and treated separately, while the soluble portion is analysed in the manner described.

Procedure.—(i) *One-way method.* Any number of mixtures can be analysed simultaneously providing that the drops of solution (approx. 0·02 c.c.) are placed at least 4 cm. apart on the starting line, which is pencilled about 8 cm. from the top edge of the paper. Two similar sheets are placed one on each side of the trough, with the top edge dipping into the liquid. Thus, with our largest tank, taking four papers 27 cm. wide, it is possible to analyse seven different mixtures at the same time in quadruplicate.

When a completely unknown mixture is analysed we prefer to chromatograph at least four spots, divide the paper afterwards into strips, spray two with our general reagents, and then use confirmatory tests on the others at the places where, from the information gained from the first strip, we know the cations to be.

For certain groups of cations a single chromatogram with a particular solvent will yield sufficient evidence for a complete analysis, but where the cations are completely unknown, it is possible to obtain three chromatograms separately with the three solvents in different tanks and compare the results. The latter method has been used very successfully for powders similar to those used in analytical courses.

Where the amount of material is strictly limited, it is practicable to separate some cations with the butanol mixture, and then after washing the paper with carbon tetrachloride and drying, to separate others with the dioxan mixture. Only a few such separations have been carried out; the method is capable of further development.

(ii) *Two-way method.* The analysis of one drop (0·02 c.c.) of solution is achieved by separating some of the cations by the collidine, and the others at right angles to the original direction with the butanol mixture. On a piece of filter-paper (27 cm. square) two lines are drawn at right angles, 8 cm. from the edge of the paper. One drop of solution is placed at the point of intersection, and then chromatographed with the collidine mixture. The paper is removed from the tank, washed with carbon tetrachloride, dried in air, and then chromatographed with the butanol mixture run at right angles to the collidine direction.

A still better separation for some cations can be obtained by washing and drying the paper as described above and then running it with dioxan in the same direction as the butanol.

Since two papers can be used in each tank, one of the chromatograms can be tested with the general spraying reagents, and the other used for confirmatory tests.

Results.

Examples of Mixtures separated and identified. (Other possible separations can be predicted from Table I, Part I.)—(I) *One-way, one-solvent mixture chromatograms.* (*a*) With butanol–water containing benzoylacetone: (i) As, Hg, and Pb. (ii) Hg, As, Fe, and one of the following: Ag, Pb, Bi, Al, Cd, Mn, Co, Ni, Ca, Sr, Ba, Mg, K, or Na. (iii) Cu, As, Fe, and one of the following: Ag, Zn, Mn, Co, Bi, Ni, Ca, Sr, Ba, Mg, K, or Na. (iv) Pb, Cd, Cu, As, and Fe. (v) Hg, Bi, Cu, and Cd. (vi) As, Sb, and Sn.

(*b*) With collidine mixture: (i) Pb and Ag or Zn. (ii) Hg and Cd or Zn. (iii) Bi and Cd. (iv) Cu and Hg, or Fe, or Zn. (v) Co and Ni. (vi) Zn, Mn, Co, and Ni. (vii) Ca, Ba, and Sr. (viii) Mg, K, and Na. (ix) Ca, K, and Na. (x) Mg, Ca, K, and Na. (xi) Zn, Mg, Ca, Sr, and Ba. (xii) Mn, Mg, K, and Na. (xiii) Zn, Mg, Ca, K, and Na.

(*c*) With dioxan mixture containing antipyrine: (i) Ag, Hg, and Pb. (ii) Cu, Hg, and Bi, with Ag, or Pb, or Al, or Zn. (iii) Cd, Hg, and Bi, with Al, or Zn, or Co, or Ca, or K. (iv) Fe and Bi. (v) Cu, Bi, and Mn or Ni, or Mg.

The relative positions of the individual cations can be ascertained from Table I (see Part I), except where some interference occurs. All the above move according to the predictions, except for (i) As, Sb, and Sn, where the R_F values after separation with butanol are 0·40, 0·53, and 0·63, respectively, while the individual cations have R_F values of 0·43, 0·0, and 0·54; and (ii) Zn, Mn, Co, and Ni, where the R_F values after separation with collidine are 0·77, 0·75, 0·80, and 0·82 which, with this displacement effect, causes the Zn, Co, and Ni to appear as transverse bands. The separation of Cu and Fe with the dioxan solvent mixture has not been possible owing to displacement; the cationic mixture moves with a common R_F value of 0·4 whilst the individual cations move with the following R_F values: Cu, 0·24 and Fe, 0·09.

It will be observed that the Ag, Hg, and Pb mixture has been separated by both the butanol and the dioxan solvent. The latter gives better and more rapid separations—with Whatman No. 1 in 5 hours, or Whatman No. 54 in less than one hour. The rapid movement of the solvent does not affect the formation of symmetrical concentrated spots.

A further possible adaptation of these methods consists of comparison of three separate chromatograms, using the three general solvent mixtures. The advantage of this is that the three experiments can be run simultaneously in separate tanks with a saving of time, and as some cations move in two or more solvents, confirmatory evidence of the presence of a particular cation can be obtained from the different chromatograms. The collidine solvent mixture furnishes definite evidence of the presence of the following cations: Ag, Al, Fe, Cd, Zn, Na, K, Ca, Ba, and Sr; the butanol mixture containing benzoylacetone of Cu, Cd, As, Sn, Fe; and the dioxan with antipyrine of Ag, Pb, Cu, Cd, Fe, Hg, Bi, Co, and Ni. Where, as with Cd and Zn, Co and Ni, there is likelihood of uncertainty since there is insufficient separation on the chromatogram and the general spraying reagents yield similar spots, it is possible to identify the particular cation by a suitable spot reagent. It is also unlikely that there will be more than eight different cations present in any particular mixture for analysis.

This scheme was tested on 20 unknown mixtures chosen at random from those normally issued to students in the analytical course. The cations were mixed in all kinds of proportions, and associated with many different anions. Sometimes a cation was missed because the amount present was below the sensitivity of the method, and in other cases the presence of certain anions seemed to interfere with the movement of cations. Hence, though this method was not in every analysis completely successful, it can be said that no cation was reported that was not present in the powder though it was possible to miss a cation either through interference or because it was present in extremely small amounts. Methods of overcoming these difficulties are being investigated.

(II) *One-way, two solvents used consecutively on the same chromatogram.* This procedure was tried with a mixture of Al, Bi, and Fe, first chromatographing it with the butanol mixture containing benzoylacetone, washing the paper with carbon tetrachloride, and drying, and then chromatographing it in the same direction with the dioxan mixture containing antipyrine. With the first solvent mixture, Fe moved, leaving the Bi and Al near the starting line, and then with the second solvent the Bi separated from the Al. The R_F values after movement were Fe, 0·95; Bi, 0·6; and Al, 0·06; thus, there was very clear and distinct separation of these three cations. It is possible to apply this technique to many other similar mixtures of cations.

(III) *Two-way, two-solvent mixtures.* First solvent—collidine; second solvent—butanol. Examples of separations achieved: (i) Cu, As, and Fe with any of the following: (*a*) Pb and Zn, (*b*) Pb and Mn, (*c*) Pb, Zn, and Mn, (*d*) Pb, Cu, Mn, (*e*) Al and Cd, (*f*) Al and Mn, (*g*) Al, Cd, and Mn, (*h*) Al, Zn, and Mn. (ii) Al, Cu, Fe, Zn, Ca, and Mg. (iii) Pb, Cu, Cd, Fe, Ca, Sr, Ba. (iv) Bi, Cu, Fe, Co, Mg, K, and Na. (v) Pb, Cu, Fe, Zn, Mn, Ca, and Mg.

The positions of these cations after movement are usually in accordance with the prediction from their movements in the two separate solvent mixtures, and are shown in the scheme below. It has been observed that Cu and Zn always have a higher R_F value in the second solvent (butanol) than would be

expected—probably owing to the stability of the respective collidine complexes. Even so, there is no difficulty in identification since it depends not only on the R_F, but also on characteristic tests. There is also a tendency for arsenic not to move in the collidine mixture if certain cations are present, and the alternative positions for it are shown in the scheme (section 1).

The general movement of the cations is along two axes at right angles, and in many cases this provides sufficient separation for analysis. However, it was thought advisable to see if still further separation could be achieved by use of the third solvent. For reasons which are not yet understood the dioxan was not satisfactory in the two-solvent procedure, but from the limited experience gained with the three-solvent procedure it has definite advantages here.

Scheme illustrating two-way separations. The chromatogram is marked into rectangles, by dividing the distances along the axes from the starting point to the respective solvent fronts into ten equal divisions. The rectangle in which the cation is expected to occur is then given by reference to the *x*-axis by letters *A* to *J*, and to the *y*-axis by numbers 1 to 10.

(IV) *Two-way, three-solvent separations.* First solvent—collidine; second solvent—butanol; third solvent—dioxan run in the same direction as butanol.

With a mixture of Al, Bi, Mg, Mn, Cd, and Cu, the separations with this procedure are illustrated in the scheme (section 2). With the first two solvents the cations moved to the positions expected (scheme, section 1); there was almost no separation of Al and Bi. When the third solvent, dioxan, was used, the Bi separated from the Al, and Mg, Mn, and Cd moved to new positions well separated from one another. It would seem, therefore, that for certain groups of cations the three-solvent technique will be quite useful.

The foregoing two-way separations are summarised in the accompanying scheme.

(1) Two-way separations with (*a*) collidine, *x*-axis, and (*b*) butanol containing benzoylacetone, *y*-axis: Al, Bi, Pb, [*A*, 1]; Ba, [*C*, 1]; K, Sr, [*D*, 1] or [*E*, 1]; Na, [*E*, 1]; Ca, [*F*, 1]; Mg, [*G*, 1]; Mn, Cd, [*H*, 1]; Zn(a), [*I*, 1]; As(a), [*A*, 4]; As(b), [*F*, 4]; Hg^{2+}, [*A*, 6]; Cu, [*H*, 8]; Fe, [*A*, 9].

(2) Two-way separations with (*a*) collidine, *x*-axis, and (*b*) benzoylacetone in butanol, followed by antipyrine in dioxan, *y*-axis: Al, [*A*, 2]; Mg, [*E*, 2]; Mn, [*F*, 2]; Cd, [*G*, 3]; Bi, [*A*, 5]; Cu, [*G*, 8].

Special Separations.—Although we have paid rather more attention to the development of a general method of qualitative analysis, certain solvents other than those used in our general procedure have advantages for special separations, and these are described below. All the cations have been detected with our general fluorescent reagent.

Separation of Cd *and* Zn. The best separation of these two cations has been observed with a mixture of butanol, 0·1N-nitric acid, and collidine (5 : 4 : 1). The R_F values were: Cd 0·24, Zn 0·06, and good, symmetrical, concentrated spots were obtained.

Separation of Th *and* U. A mixture of these two cations as nitrates can be separated with a mixture of butanol–N-nitric acid (1 : 1) and 0·5% benzoylacetone. The R_F values for the mixture are: Th 0·03 and U 0·27.

Separation of K, Ti, V, Mo, *and* Fe. A solution of these cations was prepared by mixing equal volumes of 2% solutions of titanium potassium oxalate, vanadium chloride, ferric nitrate, and ammonium molybdate. With a solvent mixture consisting of butanol–N-nitric acid (1 : 1) and 1% acetylacetone, the individual cations were found to have the following R_F values: K 0·07, Ti, 0·60, V 0·20, Mo 0·58, and Fe 0·54, from which one would deduce that a satisfactory separation of Ti, Mo, and Fe is not probable. However, with the mixture of cations the R_F values become K 0·07, Ti 0·55, V 0·17, Mo 0·63, Fe 0·40, which leads to a very satisfactory chromatogram.

Separation of Mo *from other cations.* The importance of molybdenum in agricultural research led us to investigate the behaviour of mixtures containing this element, and we have found that the collidine mixture enables one to separate molybdenum, originally as molybdate, from those elements with which it is usually associated. Its R_F value as an individual ion is 0·24, but it does not always move in the same way with different ions: nevertheless, it can be readily identified.

The following mixtures have been satisfactorily analysed, though the cations do not all move with their normal R_F values, which are quoted in parentheses wherever any marked difference occurs: (*a*) Fe 0; Mo 0·20 (0·24); As 0·60 (0·64); and Co 0·75. (*b*) Pb 0; Mo 0·20 (0·24); K 0·33; Zn 0·76. (*c*) Al 0; Mo 0·18 (0·24); K 0·31; Mg 0·49 (0·64); Cu 0·76. (*d*) Fe 0; Mo 0·19; Ca 0·37 (0·54); Mg 0·47 (0·64); Zn 0·65 (0·75); Co 0·75. All these mixtures give distinct chromatograms and good symmetrical spots; the slight displacements which occur tend to improve the separations.

Separation of anions. (With Mr. A. B. Law.) A number of suggestions have been made by other workers (*e.g.*, Lederer, *Roy. Aus. Chem. J.*, 1950, **17**, 308) for the separation of certain groups of anions. Using a similar procedure to that described for a study of the individual cations, we have investigated the behaviour of the following anions: chloride, bromide, iodide, thiocyanate, chlorate, bromate, iodate, carbonate, chromate, sulphate, nitrate, nitrite, orthophosphate, arsenite, and arsenate, with a number of different solvent mixtures. We used generally the sodium or potassium salts, and where convenient, the free acid. The solvent mixture was found to be most successful when it was alkaline, and the best movement and spots were obtained with a solvent mixture consisting of butanol, pyridine, and 1·5N-ammonia (2 : 1 : 2). The anions were found to move with the following R_F values: chloride 0·24, bromide 0·36, iodide 0·47, chlorate 0·42, bromate 0·25, iodate 0·09, nitrite 0·25, nitrate 0·40, arsenite 0·19, arsenate 0·05, carbonate 0·06, phosphate 0·04, chromate 0·00, thiocyanate 0·56, sulphate 0·07.

Many reagents were investigated as sprays for their suitability in the detection of anions. The most generally useful reagent was ammoniacal silver nitrate, but certain reagents were particularly good for special groups, *e.g.*, potassium iodide and hydrochloric acid for chlorates, bromates, and iodates.

Mixtures of some of the anions were tried and in all cases the movement and separation were almost the same as for the individual anions; the slight displacements observed, *e.g.*, with NO_3, Br, and I, tended to improve the chromatographic separation. The most successful separations were with the following :

(i) Chloride with iodide, or bromide and iodide, or thiocyanate, or nitrate and thiocyanate. (ii) Bromide with nitrate or thiocyanate. (iii) Iodide with nitrate. The other separations possible with this solvent are apparent from the R_F values.

A test was made to find if the anion moved independently of the cation with nitric acid, hydrochloric acid, sulphuric acid, sodium nitrate, lead nitrate, potassium nitrate, sodium chloride, potassium chloride, sodium sulphate, and potassium sulphate. In all cases the anion moved with the same R_F value, while the cation either stayed on the starting line or moved slightly.

A comparison of the potassium salts of the various anions which moved appreciably showed that, after being sprayed with naphthylaminesulphonic acid and viewed under the ultra-violet lamp, the potassium spot was brightly fluorescent with an R_F of 0·12, while the anions gave black spots and had moved to their normal positions, further down the chromatogram.

Further work is in progress to develop a general procedure for the analysis of groups of anions.

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103. *Pteridine Studies. Part I. Pteridine, and 2- and 4-Amino- and 2- and 4-Hydroxy-pteridines.*

By ADRIEN ALBERT, D. J. BROWN, and GORDON CHEESEMAN.

Syntheses of pteridine and a number of mono-substituted pteridines are reported, including a new route to the pteridine series from pyrazine intermediates. Solubilities, ionization constants, and ultra-violet spectra are recorded and discussed from the point of view of comparative heterocyclic chemistry.

The value of paper chromatography as well as ultra-violet spectroscopy for following the purification of non-melting pteridines is emphasized. 4-Hydroxypteridine has marked chelating affinity for the cations of heavy metals, a finding that is likely to be of significance in the living cell. The relative chemical stability of individual pteridines is discussed.

Syntheses of a number of pyrazines and pyrimidines, required as intermediates, are described.

PTERIDINE derivatives were found in Nature as long ago as 1889, but their constitution remained baffling until Purrmann in 1940 showed that xanthopterin and leucopterin are aminopolyhydroxy-derivatives of the (then) unknown substance pyrimidino-4′ : 5′-2 : 3-pyrazine (I) to which Wieland then gave the name pteridine. More pteridines have since been recognized in Nature, notably folic acid which plays an important part in hæmatopoiesis and cell-division.

All natural pteridines have at least one amino- *and* one hydroxy-substituent. As no monohydroxy- or monoamino-pteridine was known, it was decided to synthesize all of them and to investigate the connexions between structure, physical properties, and biological activity in the pteridine series. This approach was suggested by the success achieved in revealing the chemical basis of antisepsis by aminoacridines and by hydroxyquinolines through similar exploration of all possible mono-isomerides (Albert, Rubbo, Goldacre, Davey, and Stone, *Brit. J. Exper. Path.*, 1945, **26**, 160; Albert, Rubbo, Goldacre, and Balfour, *ibid.*, 1947, **28**, 69). The present paper is mainly concerned with pteridines substituted in the pyrimidine ring.

(I.) (II.) (III.) (IV.)

Syntheses.—Hitherto, with one exception, all the known pteridines have been prepared by condensing 4 : 5-diaminopyrimidines (*e.g.*, IV) with carbonyl compounds or their derivatives. The exception was the synthesis of 2 : 4-dihydroxypteridine in 40% yield by the action of potassium hypobromite on pyrazine-2 : 3-dicarboxyamide (Gabriel and Sohn, *Ber.*, 1907, **40**, 4857). Some new syntheses, using pyrazine intermediates, are now described. 2-Amino-

pyrazine-3-carboxyamide (II) when refluxed with ethyl orthoformate gave 4-hydroxypteridine (III) in 75% yield, and (III) was also obtained from (II) by acetic anhydride–formic acid and from the formyl derivative of (II) by sodium ethoxide. Likewise 2-aminopyrazine-3-carboxythioamide and ethyl orthoformate gave 4-mercaptopteridine in excellent yield. Some unsuccessful attempts to devise other syntheses of pteridines from pyrazines are recorded in the Experimental section.

Pteridine and the following new pteridines were obtained by condensing 4 : 5-diaminopyrimidines (*e.g.*, IV), with glyoxal or glyoxal sodium bisulphite : 2-amino-, 2-dimethylamino-, 4-amino-, 2-hydroxy-, 4-hydroxy-, and 2-chloro-pteridine; 4-hydroxy-6 : 7-dimethylpteridine was similarly obtained by use of diacetyl. Glyoxal sodium bisulphite appears to give dihydropteridinesulphonic acids analogous to the dihydroquinoxalinesulphonic acids which are similarly formed (Bergstrom and Ogg, *J. Amer. Chem. Soc.*, 1931, **53**, 245) and these have to be broken down to pteridines with acid or alkali.

The only recorded synthesis of pteridine involves the reaction of 4 : 5-diaminopyrimidine with glyoxal sodium bisulphite in aqueous solution (Jones, *Nature*, 1948, **162**, 524; no details or yield given). In our experience, no higher yield than 15% could be obtained in this way; this was increased to 50% when the condensation was carried out in alcohol using commercial syrupy glyoxal and to 63% by using the polyglyoxal that had deposited in an old bottle of the syrup.

4-Hydroxypteridine was prepared in yet a third way: by the alkaline hydrolysis of 4-aminopteridine.

Purity.—Because most pteridines decompose at high temperatures without melting sharply, special reliance has been placed upon three criteria: purification (i) to constant solubility (in water), (ii) to constant spectral properties, and (iii) until only one spot appears on paper-chromatography. For the last, a mixture of butanol and aqueous acetic acid has been found most discriminatory (see Experimental section) and the R_F values thus obtained are listed in Table I. As an example of the value of (iii), the paper chromatogram of 2 : 4-dihydroxypteridine, prepared according to Kuhn and Cook (*Ber.*, 1937, **70**, 761) "in schönen gelben Nädelchen," or according to Cain, Mallette, and Taylor (*J. Amer. Chem. Soc.*, 1946, **68**, 1996), initially revealed 5 spots. We purified this substance by repeated crystallization after boiling it with relatively large amounts of alumina until only one spot remained on paper chromatography. The substance then consisted of white crystals, 2 mm. long, giving correct analytical figures, as the yellow specimen of Kuhn and Cook had done. Hence it is doubtful if this substance had previously been obtained pure: Polonovski, Vieillefosse, and Pesson (*Bull. Soc. chim.*, 1945, **12**, 78) describe their specimen as pale yellow, and the extinction coefficients recorded by Cain, Mallette, and Taylor (*loc. cit.*) are only 72—76% of those given by the present material.

Paper chromatography is very useful in this series for establishing identity by running the doubtful material alongside (or even mixed with) an authentic specimen and comparing the R_F values and the colours of the spots under ultra-violet light of different wave-lengths.

Physical Properties.—Solubility. Introduction of even one hydroxy-, mercapto-, or primary amino-group into pteridine greatly lowers the solubility (roughly one-hundredfold) (see Table I). The solubility of acridine is also lowered by the insertion of amino- or hydroxy-groups, but to a lesser degree (Albert, "The Acridines, their Preparation, Properties and Uses," London, Edward Arnold, 1951, p. 152). This effect is probably more common among hetero-aromatic bases than has been realized. It is unlikely that amino- and hydroxy-groups cease to exert their well-known water-attracting properties, but that they exert an even stronger effect on the negatively charged ring-nitrogen atoms of neighbouring molecules, an attraction which makes a far stronger crystal lattice. That this effect depends more on hydrogen-bonding than on the attraction of oppositely charged dipoles is shown by 2-dimethylaminopteridine which is 540 times as soluble in water as 2-aminopteridine. The hydroxy- and primary amino-pteridines are almost insoluble in boiling alcohol, benzene, or pyridine, whereas pteridine, 2-chloro-, and 2-dimethylamino-pteridine are highly soluble in all these solvents, even in the cold. The solubilities of the acetamidopteridines lie between those of the primary aminopteridines and of pteridine. The fact that all the known hydroxy-, (primary) amino-, and aminohydroxypteridines decompose above 240° without melting is another expression of the ability of these substituent groups to strengthen the crystal lattice. Pteridine and 2-dimethylaminopteridine, on the other hand, melt at 140° and 126° respectively, without decomposition.

Ionizing properties. Introduction of further ring-nitrogen atoms into a hetero-aromatic base usually has a base-weakening effect (Albert, Goldacre, and Phillips, *J.*, 1948, 2240). In so far as pteridine is the diaza-derivative of quinoxaline, of 1 : 8-naphthyridine, and of quinazoline

(which have pK_a values of 0·8, 3·4, and 3·5 respectively), its tendency to ionize was found unexpectedly high (pK_a = 4·1, see Table I; cf. also quinoline in Table II). Evidently a complex electronic interplay takes place between the several nitrogen atoms. The 2- and

TABLE I.

Physical properties of pteridines.

Pteridine.	Solubility (approx.) in H_2O (20—25°), 1 in :	pK_a (in water) and concentration at which determined (20°).		Spectrography in water. R_F.[2]	$\lambda_{max.}$ (mμ.).	log $\epsilon_{max.}$ (mol.).	pH.
(Unsubstituted)	7·2	—	—	0·25	<220; 298 + 309 [5]	>3·83; 3·87; 3·83	6·2
cation	—	4·12 (± 0·05)	M/20	—	<220; 300	>3·84; 3·92	1·1 or 2·1
2-Amino-	1350	—	—	0·70	225; 370	4·38; 3·82	7·1
cation	—	4·29 (±0·03)	M/100	—	<210; 302	>4·04; 3·87	2·1
4-Amino-	1400	—	—	0·70	244; 335	4·20; 3·82	7·3
cation	—	3·56 (±0·08)	M/200	—	229; 324	4·10; 3·99	1·1
anion	—	>14	—	—	(see graph)	—	—
2-Dimethylamino-	2·5	—	—	0·90	236; 281; 410	4·37; 4·02; 3·82	7·1
cation	—	3·03 (±0·02)	M/100	—	237; 305	4·16; 3·90	1·0
2-Hydroxy- (+1H_2O)	600	—	—	0·80	230; 307	3·88; 3·83	7·1
anion	—	11·13 (±0·05)	M/100	—	260; 375	3·85; 3·78	13
cation	—	<2	M/100	—	—	—	—
4-Hydroxy-	200	—	—	0·50 [4]	230; 265; 310	3·98; 3·54; 3·82	5·6
anion	—	7·89 (±0·03)	M/100	—	242; 333	4·23; 3·79	10·0
cation	—	<1·5	M/100	—	—	—	—
4-Hydroxy-6 : 7-di-methyl-	1100	—	—	0·60	230; 270; 313	4·03; 3·67; 3·93	6·2
anion	—	8·39 (±0·03)	M/200	—	—	—	—
2 : 4-Dihydroxy- (lumazine)	800	—	—	0·50	230; 324	4·00; 3·84	5·9
anion (mono-)	—	7·91 (±0·07)	M/100	—	235; 270; 347	4·02; 3·95; 3·69	10·1
anion (di-)	—	—	—	—	252; 365	4·23; 3·78	13
cation	—	<1·0	M/20	—	—	—	—
2-Amino-4-hydroxy-	57,000	—	—	—	—	—	—
anion	—	(approx. 8·0) [1]	—	—	252; 359	4·30; 3·83	13
2-Amino-4 : 6-dihydroxy (xanthopterin) (+1H_2O)	40,000	—	—	—	—	—	—
anion (mono; 6-position)	—	6·25	M/1000 [3]	—	—	—	—
anion (di; 4- and 6-positions)	—	9·23 (±0·04)	M/1000 [3]	—	255; 392	4·27; 3·85	13
2-Amino-4 : 6 : 7-trihydroxy- (leucopterin)	750,000	—	—	—	—	—	—
anion	—	—	—	—	240; 285; 340	4·20; 3·84; 4·02	13
2-Mercapto (+1H_2O)	1400	—	—	—	<215; 270; 315	>3·74; 4·24; 4·22	7·1
anion	—	9·98 (±0·05)	M/200	—	—	—	—
4-Mercapto-	3600	—	—	0·70	256; 390	4·13; 4·00	4·1
anion	—	6·81 (±0·02)	M/600	—	265; 408	4·22; 3·93	13

[1] Stokstad *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 5. [2] Back-titrated. [3] Solvent : BuOH–AcOH. [4] A small extra spot at 0·30 is seen on paper giving an ash rich in iron and copper; this is not seen if 8-hydroxyquinoline is allowed to travel ahead of the 4-hydroxypteridine. [5] Fine structure.

4-aminopteridines (Table I) are bases of approximately the same strength as pteridine. Thus they do not show the exaltation of basic strength through ionic resonance which is such a feature of 2- and 4-aminoquinolines, but which was found to decline in intensity with the addition of a further ring-nitrogen atom to give aminoquinazolines (Albert, Goldacre, and Phillips, *loc. cit.*).

When a concentrated (colourless) solution of 4-aminopteridine is added to an excess of 0·2N-sodium hydroxide, a yellow colour appears (see Fig. 4). When the solution is neutralized the spectrum of the neutral molecule is restored. The colour appears to reach a maximum in 5N-sodium hydroxide, but hydrolysis to 4-hydroxypteridine is then rapid. The colour change clearly indicates that 4-aminopteridine can form an anion; no similar phenomenon has ever been reported for the aminoquinolines or their analogues containing more ring-nitrogen atoms.

4-Hydroxypteridine and its derivatives are, as would be expected, stronger acids (pK_a *ca.* 8) than 4-hydroxyquinoline and 4-hydroxyquinazoline (pK_a = 12·4 and 10·0 in 50% alcohol; Keneford, Morley, Simpson, and Wright, *J.*, 1949, 1356). A pK_a of 8·26 ± 0·06 found for folic acid (M/500) is apparently that of the 4-hydroxy-group in the pteridine nucleus. 2-Hydroxypteridine is a weaker acid than its 4-isomeride but no figures are available for the corresponding quinoline and quinazoline derivatives. 2- and 4-Mercaptopteridines are stronger than their hydroxy-analogues by about 1 unit of pK. Potentiometric titration of the most concentrated solutions possible failed to disclose any basic properties in 2- and 4-hydroxypteridines, down to pK_a 1·5. This is an outstanding example of the lowering of base-strength by the insertion of a hydroxy-group in such a position as to form what may be regarded as a cyclic amide. For example, 4-hydroxyquinoline is 2·65 units of pK weaker than quinoline (Table II), 2-hydroxypyridine is 4·0 units weaker than pyridine (Stiller, Keresztesy, and Stevens, *J. Amer. Chem. Soc.*, 1939, **61**, 1237), and 4-hydroxyquinazoline is considerably weaker than quinazoline (Keneford *et al.*, *loc. cit.*). However, this effect cannot be universal, for it is not evident in 2- and 4-hydroxypyrimidines (Table II).

TABLE II.

Physical properties of some related heterocyclic substances.

Substance.	pK_a (in water) and concn. at which determined (20°).		Spectrography in water. $\lambda_{max.}$ (mμ.).	Spectrography in water. log $\epsilon_{max.}$ (mol.).	pH.
Quinoline	—	—	226 275 + 299 + 312 [3]	4·36 3·51; 3·46; 3·52	6·3 —
cation	4·94 [1]	M/60	233; 313	4·50; 3·80	1·1
Quinoxaline	—	—	234; 316	4·47; 3·79	7·1
cation	0·8 [1]	M/10	242; 331	4·44; 3·93	−2·0 [6]
Quinazoline	3·51 [1]	M/15	<220 270 + 310 [3]	>4·6 3·4; 3·3	— —
1 : 8-Naphthyridine	—	—	<225 260 + 301 + 309	<4·1 3·62; 3·80; 3·81	6·3 —
cation	3·39 (±0·01)	M/100	<215 302 + 309	>4·1 4·02; 4·01	1·0 —
4-Hydroxyquinoline	—	—	—	—	—
cation	2·29 (±0·05)	M/10	—	—	—
Pyrimidine	—	—	243	3·5; 2·5	—
cation	1·30 [1]	M/15	—	—	—
2-Hydroxypyrimidine	—	—	215; 299	4·00; 3·66	6·1
cation	2·24 (±0·04)	M/10	<210; 309	>3·9; 3·75	0·3
anion	9·17 (±0·06)	M/100	<230; 290	>4·1; 3·66	13
4-Hydroxypyrimidine	—	—	225	3·83	6·3
cation	1·85 (±0·04)	M/10	225	4·00	0·3
anion	8·59 (±0·02)	M/30	229; 265	4·07; 3·68	13
Pyrazine	0·6 [1]	M/10	256 + 260 311 + 316 [4]	3·68; 3·72 2·76; 2·75	— —

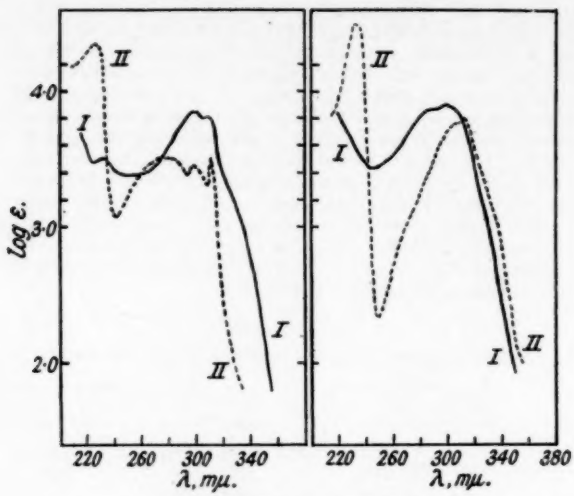
[1] Albert, Goldacre, and Phillips, *J.*, 1948, 2240. [3] Fine structure. [4] Neutral molecule in alcohol; Elderfield, Williamson, Gensler, and Kremer, *J. Org. Chem.*, 1947, **12**, 405. [6] Heyroth and Loofbourow, *J. Amer. Chem. Soc.*, 1934, **56**, 1728. [5] In alcohol; Barany, Braude, and Pianka, *J.*, 1949, 1898. [6] 7·76N-H_2SO_4.

4-Hydroxypteridine and its derivatives form stable chelate compounds with cupric, nickel, cobaltous, zinc, ferrous (but not ferric), cadmium, and manganous ions (Albert, *Biochem. J.*, 1950, **47**, ix). All naturally-occurring pteridines contain a 4-hydroxy-group; hence this affinity for the ions of heavy metals probably has a biological significance.

Spectra. The spectrum of pteridine (in water) is shown in Fig. 1, with that of quinoline. A certain similarity is to be expected because =CH− and =N− are to a large extent optically interchangeable (Braude, *Ann. Reports*, 1945, **42**, 129). For example, the spectra of anthracene, acridine, and phenazine (Radulescu and Ostrogovich, *Ber.*, 1931, **64**, 2233) are almost identical, but each nitrogen atom causes a partial loss of detail. Consistently, the spectra (Table II) of quinazoline, quinoxaline, and 1 : 8-naphthyridine are similar. As with quinazoline, the short-wave absorption of pteridine has been displaced to shorter wave-lengths where it cannot be completely traced. In *cyclo*hexane, the spectrum of pteridine reveals no additional fine structure.

When quinoline is converted into the cation, both absorption regions are intensified and shifted slightly to longer wave-lengths. The changes occurring when pteridine ionizes are similar but less (Fig. 2).

FIG. 1. FIG. 2.

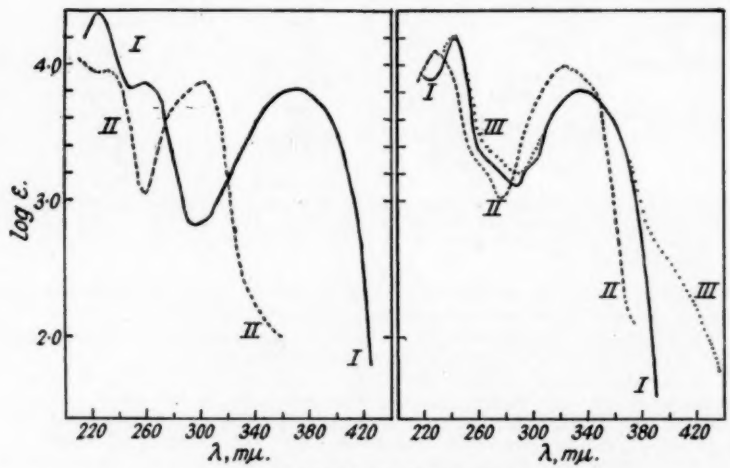


Absorption spectra in water of

I. Pteridine (pH 6·2).
II. Quinoline (pH 6·3).

I. The cation of pteridine (pH 2·1).
II. The cation of quinoline (pH 1·1).

FIG. 3. FIG. 4.



Absorption spectra in water of

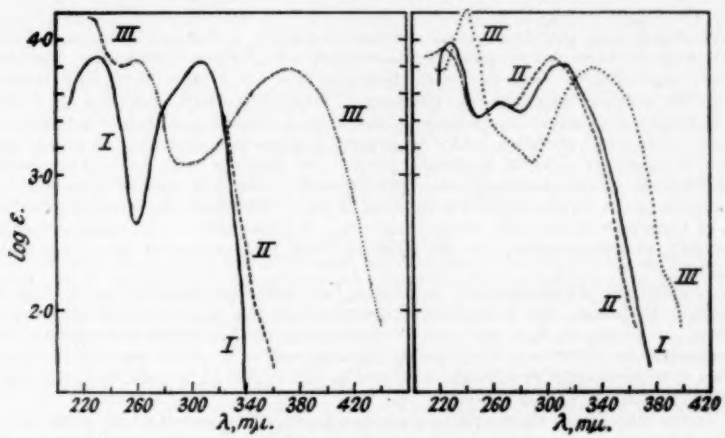
I. 2-Aminopteridine (pH 7·1).
II. The cation of 2-aminopteridine (pH 2·1).

I. 4-Aminopteridine (pH 7·3).
II. The cation of 4-aminopteridine (pH 1·1).
III. The anion of 4-aminopteridine (0·2N-NaOH). *This curve merges with that of the neutral molecule where not shown separately.*

The spectra of 2- and 4-amino- and 2- and 4-hydroxy-pteridines (as neutral molecules) closely resemble that of pteridine itself. The principal difference is that one or both of the absorption regions is shifted to longer wave-lengths, as is usual for amino- and hydroxy-derivatives. The spectrum of the parent substance is less disturbed by the hydroxy- than by the amino-group, but the spectra of the anions of the hydroxy-compounds closely resemble the spectra of the neutral molecules of the corresponding amines. This is usual among the amines and phenols derived from aromatic hydrocarbons (Jones, *J. Amer. Chem. Soc.*, 1945, **67**, 2127), yet 2- and 4-hydroxyquinolines show relatively little change on ionization as anions (Ewing and Steck, *J. Amer. Chem. Soc.*, 1946, **68**, 2181). The spectrum of 4-hydroxypteridine in 93% v/v alcohol was almost identical with that in water; apparently the lowering of dielectric constant did not bring about the ketamine–enimine tautomerism so readily effected in 2- and 4-hydroxy-acridines (Albert and Short, *J.*, 1945, 760). A small shoulder in the spectrum of pteridine at 235 mμ. is apparently the source of a similar area in 2-amino- and 4-hydroxy-pteridines (cf. Figs. 1, 3, and 6).

Ionization as cations causes a shift of the absorption of 2- and 4-aminopteridines to much

FIG. 5. FIG. 6.



Absorption spectra in water of

I. 2-*Hydroxypteridine* (pH 7·1).
II. 2-*Hydroxypteridine at* pH 0·3.
III. The anion of 2-*hydroxypteridine* (pH 13).

I. 4-*Hydroxypteridine* (pH 5·6).
II. 4-*Hydroxypteridine at* pH 0·3.
III. The anion of 4-*hydroxypteridine* (pH 10·0).

shorter wave-lengths. The reverse happens for 2- and 4-aminopyrimidines (Stimson, *J. Amer. Chem. Soc.*, 1949, **71**, 1470; Williams, Ruehle, and Finkelstein, *ibid.*, 1937, **59**, 526), and no similar case has been recorded for a hetero-aromatic base although there is a hint of it in the spectra of 2- and 4-aminoquinolines, alone of the seven aminoquinolines (Steck and Ewing, *J. Amer. Chem. Soc.*, 1948, **70**, 3397). Such hypsochromy is typical of true aromatic amines (*e.g.*, the naphthylamines), but the aminopteridines cannot be diazotized and coupled.

The effect on the spectrum of the anion of 4-hydroxypteridine when further hydroxy- or amino-groups are added is shown in Table I to be bathochromic (least so in the case of leucopterin).

As with 2- and 4-mercaptoquinolines (Hannan, Lieblich, and Renfrew, *J. Amer. Chem. Soc.*, 1949, **71**, 3733) the absorption maxima of 2- and 4-mercaptopteridines (Table I) are at longer wave-lengths than those of the corresponding hydroxy-derivatives.

Pyrazine, pyrimidine, and 2- and 4-hydroxypyrimidines may be thought of as constituent parts of the hydroxpteridine molecule. However, their spectra (Table II) shed little light on those of pteridine and the hydroxypteridines.

Fluorescence. Unlike xanthopterin, pteridines substituted only in the pyrimidine ring do

not, for the most part, fluoresce in daylight. The colours seen in ultra-violet light are given in Table III.

TABLE III.

Fluorescence in dilute aqueous solution observed by the light of a Wood's lamp (principally 360 mμ.)

Pteridine.	Water.	0·05N-NaOH.	0·05N-H_2SO_4.
(Unsubstituted)	Violet ++	Blue ++	Yellow +
2-Amino-	Green ++	Green ++	Blue ++
4-Amino-	Violet +	Violet ++	Yellow ++
2-Hydroxy-	Violet ++	Blue ++	Blue +++
4-Hydroxy-	Violet ++	Blue +	Little or none
2 : 4-Dihydroxy-	Blue +++	Blue +++	Little or none
2-Amino-4-hydroxy-	Violet +++	Violet +++	Yellowish-green +
Xanthopterin	Yellowish-green ++++	Green ++++	Yellow ++

Stability of Pteridine Nucleus.—Pteridines are unstable unless substituted elsewhere than in the 2-position. Pteridine, 2-hydroxy-, 2-amino-, 2-dimethylamino-, and 2-mercaptopteridines gave blue or violet colours in cold 10N-hydrochloric acid, even in the absence of oxygen; the original substance could not be recovered after neutralization. This colour change was most rapid with 2-hydroxy- and 2-amino-pteridines (2 minutes) but in concentrated sulphuric acid the change was almost instantaneous for all these substances. Pteridine was completely destroyed by boiling it with 2M-oxalic acid for 5 minutes or with N-potassium hydroxide for an hour (ammonia was liberated). When 2-hydroxy-, 2-amino-, or 2-dimethylamino-pteridines were boiled for a minute with N-sodium hydroxide, a deep blue or green colour developed. 2-Hydroxypteridine, added to aqueous sodium dithionite, gave an orange solution. Pteridine is sensitive to light, becoming purple; an aqueous solution of 2-aminopteridine begins to deposit an orange precipitate when exposed to sunlight, and an apparently similar decomposition occurs on prolonged drying in air at 125°. Pteridine was strongly adsorbed on a column of alumina * from a 1% benzene solution. Elution with 1 : 1 benzene–ether rapidly removed 25% of the pteridine, but the remainder had been converted into a red methanol-soluble oil.

4-Aminopteridine was completely converted into 4-hydroxypteridine by boiling it with 0·01N-sodium hydroxide for 3 minutes (4-hydroxypteridine withstands boiling 6N-sodium hydroxide). 4-Aminopteridine was partly hydrolysed, by boiling 5N-hydrochloric acid, to 4-hydroxypteridine which was itself partly decomposed to a violet substance under these conditions. When 4-hydroxypteridine was kept at pH 1 (20°) for a week, spectrography then indicated that about 10% had been destroyed.

Just as the stability of the pteridine nucleus is increased by substitution in the 4-position, so it is further increased by substitution in both the 2- and the 4-position. For example, 2 : 4-dihydroxypteridine was unchanged by boiling 10N-hydrochloric acid or 6N-sodium hydroxide.

Specific Chemical Reactions.—Pteridine readily reacted with perphthalic acid to give a *N*-oxide. Pteridine was recovered unchanged after treatment with one equivalent of nitric acid in glacial acetic acid at 20°. 4-Hydroxypteridine was destroyed when nitration was attempted in acetic acid; 4-aminopteridine survived this treatment unchanged but was entirely destroyed on dissolution in a mixture of sulphuric and fuming nitric acids. Attempts to aminate pteridine by sodamide in diethylaniline were unsuccessful. 2-Chloropteridine was easily hydrolysed to 2-hydroxypteridine by boiling water (autocatalysis by the hydrogen chloride liberated).

2- and 4-Aminopteridines were acetylated normally, but the hydroxypteridines resisted acetylation and benzoylation, even in the presence of pyridine or perchloric acid, or as the sodium salt. 2-Aminopteridine was destroyed on attempted diazotization by a method which successfully converted 2-amino-4-hydroxy- into 2 : 4-dihydroxy-pteridine (Taylor and Cain, *J. Amer. Chem. Soc.*, 1949, **71**, 2538). 4-Aminopteridine did not give 4-chloropteridine on diazotization in 10N-hydrochloric acid, a method that succeeds in the purine series (Kögl, Want, and Salemink *Rec. Trav. chim.*, 1948, **67**, 29). Boiling phosphorus oxychloride completely destroyed 2- and 4-hydroxy- and 2 : 4-dihydroxy-pteridine, although 2-amino-4-hydroxy-6 : 7-diphenylpteridine can be converted into its 4-chloro-analogue by this method in 81% yield (Cain, Taylor, and Daniel, *ibid.*, 1949, **71**, 892).

2- and 4-Hydroxypteridines gave ammonia, but no pteridine, when distilled over zinc

* Aluminium oxide " for chromatographic adsorption analysis," British Drug Houses Ltd. This is a highly alkaline preparation (cf. Cahn and Phipers, *Nature*, 1937, **139**, 717).

dust. Likewise 4-hydroxypteridine was destroyed by 2% sodium amalgam in water at 100° or by sodium in boiling amyl alcohol.

2- and 4-Hydroxypteridines were destroyed by phosphorus pentasulphide in boiling xylene. 4-Amino-2-mercaptopteridine was not changed by refluxing it with Raney nickel in aqueous ammonia, whereas 2-mercapto- and 4-hydroxy-2-mercapto-pteridines were destroyed; yet this method smoothly replaces –SH by –H in the pyrimidine series (Brown, *J. Soc. Chem. Ind.*, 1950, in the press). Finally 4-aminopteridine was not converted into 4-mercaptopteridine by boiling N-potassium hydrogen sulphide or by hydrogen sulphide at pH 4—5, methods similar to those found useful in the acridine series (Asquith, Hammick, and Williams, *J.*, 1948, 1181).

These results emphasize that substitutents are best introduced (for the simpler pteridines at east) *before* ring-closure.

Experimental.

(M. p.s are uncorrected. Microanalyses were by Mr. A. Bennett, Beckenham.)

Absorption Spectra.—These were measured in the Hilger "Uvispek" photoelectric spectrophotometer (with 4-cm. cells and dilutions of from 10^{-4} to 4×10^{-4}M. in water distilled in glass apparatus) at 5-mμ. intervals, except in the neighbourhood of peaks where 1-mμ. intervals were used.

Potentiometric Titrations.—A glass electrode with a shielded lead, and a calomel electrode having a sintered-glass diaphragm, were used with a pH set (Cambridge Instrument Company) standardized against 0·05M-potassium hydrogen phthalate (pH 3·97) and against boric acid (throughout its titratable range). Acidic groups were titrated with 0·1N-potassium hydroxide (carbonate-free) and basic groups with 0·1N-hydrochloric acid (N-hydrochloric acid, delivered from an "Agla" micrometer microburette, for the hydroxypyrimidines and 4-hydroxyquinoline, to minimize volume changes). Each pK_a value quoted is calculated from seven equidistant portions of the titration curve. The figure (*e.g.*, +0·03) following the pK_a gives the magnitude of the greatest divergence of any reading from this average.

Paper Chromatograms.—The chromatogram, prepared in *n*-butanol (2 volumes)–5N-acetic acid (1 volume), was viewed by the light of a mercury discharge lamp (Thermal Syndicate's T/M5/369E), passed through a filter (Chance Brothers, OX7/19874) so that 99% of the radiation was at 254 mμ. In most cases dark spots on a pale fluorescent background were obtained.

Pyrazine Intermediates.

2-*Aminopyrazine*-3-*carboxyamide.*—2-Aminopyrazine-3-carboxylic acid was prepared by heating the ammonium salt of lumazine (2 : 4-dihydroxypteridine) with sodium hydroxide according to Weijlard, Tishler, and Erickson (*J. Amer. Chem. Soc.*, 1945, **67**, 802). We find that lumazine, when prepared according to these authors, is actually in the form of its ammonium salt and that the yield of aminopyrazinecarboxylic acid is small if free lumazine is used.

The acid (22·2 g.) was added to a warm (40°) mixture of sulphuric acid (26 ml.; *d* 1·84) and methanol (90 ml.). After being kept for 24 hours at 20°, the mixture was warmed to 40° and stirred until a clear solution was obtained (about 5 minutes). After a further 48 hours at room temperature, the solution was gradually added to aqueous ammonia (280 ml.; *d* 0·88, stirred and cooled). The mixture was set aside at 20° for a day and filtered. The precipitate, recrystallized from boiling water (1200 ml.), had m. p. 232—235° (15·4 g., 70%) (cf. 48—52% obtained by Ellingson, Henry, and McDonald, *J. Amer. Chem. Soc.*, 1945, **67**, 1711, by a somewhat similar method). On recrystallization from anhydrous pyridine (15 parts) or water (70 parts), pale yellow crystals, m. p. 234—235° (238—239°, corr.), were obtained.

2-*Aminopyrazine*-3-*carboxyhydrazide.*—Methyl 2-aminopyrazine-3-carboxylate (1·53 g.) and hydrazine hydrate (2·8 ml. of 90% = 5 equivs.) were refluxed at 120° for 4 hours, cooled, diluted with water (5 ml.), refrigerated, and filtered, and the product was dried at 110°. The 2-*aminopyrazine*-3-*carboxyhydrazide* (93%; m. p. 205°), recrystallized from 40 parts of boiling water, gave cream-coloured crystals, m. p. 207—209°, almost insoluble in alcohol or benzene (Found: C, 39·25; H, 4·55; N, 45·6. $C_5H_7ON_5$ requires C, 39·2; H, 4·6; N, 45·7%). When an aqueous solution of this hydrazide was added to ammoniacal potassium ferricyanide at 60°, 2-aminopyrazine-3-carboxyamide was obtained in 70% yield instead of the expected 2-aminopyrazine-3-carboxyaldehyde.

The above hydrazide (1·53 g.) was shaken with dried pyridine (10 ml.) for 5 minutes, then toluene-*p*-sulphonyl chloride (3·1 g.) was added during 30 minutes and the whole shaken for an hour. The pyridine was distilled off in steam. The 2-aminopyrazine-3-carboxy-(*N'*-toluene-*p*-sulphonyl)hydrazide which separated on cooling was obtained from alcohol as a pale yellow solid (90%), m. p. 200—201° (if dried without heat); this did not give the expected 2-amino-3-formylpyrazine when heated with sodium carbonate in glycol (McFadyen and Stevens's method).

2-*Aminopyrazine*-3-*carboxythioamide.*—A slow stream of hydrogen sulphide was passed through a solution of 2-amino-3-cyanopyrazine (6·4 g.; Ellingson *et al.*, *loc. cit.*) and triethanolamine (2 g.) in ethanol (900 ml.) at 50—55° for 12 hours, a clear solution being formed. This was refrigerated overnight, and the crystalline precipitate filtered off (4·3 g.) and recrystallized from water (450 ml.) giving 3·1 g. of thioamide (m. p. 167—171°). The original filtrate was evaporated to dryness on the water-bath and the residue extracted with boiling water (400 ml.). The extract, treated with charcoal (2 g.) and cooled, gave a further crop (total yield, 5·8 g., 71%). 2-*Aminopyrazine*-3-*carboxythioamide* formed soft, bright yellow plates [from boiling water (100 parts)], m. p. 168—170°, readily soluble in dilute alkali (colourless solution) (Found: N, 36·4; S, 20·9. $C_5H_6N_4S$ requires N, 36·35; S, 20·8%).

Pyrimidine Intermediates.

4 : 5-*Diamino-6-hydroxypyrimidine-2-thiol.*—The ammonium salt of 4-amino-6-hydroxy-5-nitroso-pyrimidine-2-thiol (55 g.; Traube, *Annalen*, 1904, **331**, 71) was dissolved in N-sodium hydroxide (1250 ml.). To the cooled solution (20°), sodium dithionite (hydrosulphite) (200 g.) was added during 5 minutes, with stirring and addition of ice so that the temperature did not exceed 50°. After 15 minutes, acetic acid was added (75 ml., or enough to give pH 5). The mixture was cooled to 5° and the pale diamine was filtered off, washed with a little water, ethanol, and ether, and dried in warm air (yield 87%).

4 : 5-*Diamino-6-hydroxypyrimidine.*—To the above thiol (21 g.), dissolved in boiling water (400 ml.) and ammonia (25 ml.; *d* 0·88), Raney nickel catalyst (60 g., wet with water) was added in portions of 5—10 g., with shaking after each addition. The mixture was then refluxed for 2 hours and filtered. The nickel was washed with boiling water (200 ml.) and the washings were set aside. The main filtrate was refrigerated overnight and then filtered, giving 6·3 g. of diaminohydroxypyrimidine, m. p. 239°. Evaporation of the combined mother-liquor and nickel-washings gave further crops, one of which had to be recrystallized from water. The total yield was 76%.

4 : 5 : 6-*Triaminopyrimidine.*—This was similarly prepared from 4 : 5 : 6-triaminopyrimidine-2-thiol, by the method of Cavalieri, Tinker, and Bendich (*J. Amer. Chem. Soc.*, 1949, **71**, 533).

2 : 4-*Diamino-5-nitropyrimidine.*—2 : 4-Dihydroxy-5-nitropyrimidine (nitrouracil) was converted into 2 : 4-dichloro-5-nitropyrimidine by refluxing it with phosphorus oxychloride and diethylaniline (Whittaker, *J.*, in the press). The yield was 67% of material boiling sharply at 135°/17 mm. (Isay, *Ber.*, 1906, **39**, 250). 2 : 4-Dichloro-5-nitropyrimidine (103 g.) and phenol (820 g.) were heated under reflux at 140° (bath) while a stream of ammonia was passed into the mixture for 4 hours. The phenol was distilled off in a current of steam (10 l. of water), and the residual suspension was cooled and filtered. The crystals of 2 : 4-diamino-5-nitropyrimidine were washed with water, then with ethanol, and dried at 110°. The yield was 91%, and the m. p. 345—350°. On one occasion when a dark product was obtained, purification was readily effected by dissolution in 2N-hydrochloric acid (1 l.), treatment with carbon, filtration, and precipitation with ammonia (90% recovery). This diaminonitropyrimidine was also obtained (85%) by treating 4-amino-2-chloro-5-nitropyrimidine (see below) in the same way. These methods are more convenient than that of Isay (*loc. cit.*) which requires a sealed tube.

2 : 4 : 5-*Triaminopyrimidine.*—Finely powdered 2 : 4-diamino-5-nitropyrimidine (75 g.) was heated to 80° with water (1500 ml.), mechanically stirred. Sodium dithionite (375 g.) was added during 3—4 minutes. The resulting solution was stirred until it had cooled to 60°, then powdered anhydrous sodium carbonate (550 g.) was added as fast as frothing (controlled by amyl alcohol) permitted. The thick suspension was taken to dryness in an open basin on the water-bath. The solid was machine-ground and extracted for 20 minutes by stirred boiling ethanol (2·2 l.), which was filtered while hot. The filtrate was taken to dryness and the product re-extracted with ethanol (750 ml.) to remove sodium carbonate. The filtrate, taken to dryness, gave 2 : 4 : 5-triaminopyrimidine, m. p. 173—175° (77%). No suitable solvent for recrystallization was found and vacuum-distillation was too destructive.

4 : 5-*Diaminopyrimidine.*—4-Amino-2-chloro-5-nitropyrimidine was prepared from 2 : 4-dichloro-5-nitropyrimidine by the method of Isay (*loc. cit.*) except that the amination was effected by grinding the dichloro-compound with ice-cold aqueous ammonia. 4 : 5-Diaminopyrimidine-2-thiol was prepared from 4-amino-2-chloro-5-nitropyrimidine by sodium hydrogen sulphide (Elion and Hitchings, *J. Amer. Chem. Soc.*, 1947, **69**, 2553). This thiol (33 g.) was dissolved in water (800 ml.) containing aqueous ammonia (33 ml.; *d* 0·88) and the whole refluxed vigorously with Raney nickel catalyst (140 g., weighed wet with water) for an hour. The mixture was filtered and the filtrate was boiled again with nickel (60 g.) and ammonia (5 ml.) for 30 minutes. The mixture was filtered and the pale yellow filtrate was taken to dryness on a water-bath. The crystalline residue was extracted with boiling alcohol (275 ml.), and the extract was concentrated to 150 ml. 4 : 5-Diaminopyrimidine, m. p. 200—201° (softening at 195°), crystallized on cooling, and a second crop was obtained by concentration to 30 ml., the total yield being 66%.

4 : 5-*Diamino-2-chloropyrimidine.*—4-Amino-2-chloro-5-nitropyrimidine (14·1 g.) was suspended in methanol (1400 ml.) and shaken with Raney nickel (25 g., weighed wet) in an atmosphere of hydrogen until 5930 ml. of gas had been absorbed (18° and 769 mm.). The catalyst was filtered off and extracted with boiling methanol. The washings were combined with the filtrate, and the solvent recovered. The residue was dissolved in boiling water (350 ml.). This solution, treated with charcoal and filtered, deposited 4 : 5-diamino-2-chloropyrimidine (8·6 g.). A second crop (1·2 g.) was obtained by concentration. The total yield was 86% of colourless needles, decomposing around 220° when heated rapidly from 200°, and giving a single spot in paper chromatography (Jones, *loc. cit.*, gives m. p. 232°) (Found : N, 38·2. Calc. for $C_4H_5N_4Cl$: N, 38·8%).

4 : 5-*Diamino-2-dimethylaminopyrimidine.*—A mixture of 4-amino-2-chloro-5-nitropyrimidine (6·2 g.) and dimethylamine (50% methanolic; 17 ml.) was heated in methanol (50 ml.) for 1 hour at 100°. After cooling to 0°, the solid (6·3 g., 97%), m. p. 205—208°, was filtered off. A sample was purified by dissolution in dilute acid followed by reprecipitation with alkali, and subsequently recrystallized from ethanol (180 pts.) to give colourless 4-*amino-2-dimethylamino-5-nitropyrimidine*, m. p. 210—211° (Found : C, 39·4; H, 4·6. $C_6H_9O_2N_5$ requires C, 39·3; H, 4·95%).

This substance (6 g.; finely ground) was suspended in water (150 ml.) at 80° and sodium dithionite (45 g.) was added with mechanical stirring during 2 minutes. While the mixture was still hot, sodium carbonate (75 g., anhydrous) was added with stirring. After evaporation to dryness the purple residue was extracted with boiling ethanol (250 ml.). The filtrate, taken to dryness, gave 4 : 5-diamino-2-dimethylaminopyrimidine (3·5 g., 70%), m. p. 115—121°. Its colour was dark and because the solubilities had poor temperature gradients no attempt was made to recrystallize the material.

Pteridines from Pyrazine Intermediates.

4-Hydroxypteridine.—2-Aminopyrazine-3-carboxyamide (1·38 g., 0·01 mole), acetic anhydride (20 ml.), and ethyl orthoformate (20 ml.) were refluxed for 2 hours at 150° (bath). The mixture was taken to dryness in a vacuum and the residue was boiled for 3 minutes with N-sodium hydroxide (15 ml., or enough to give pH 10), cooled quickly to 20°, and filtered after 15 minutes. The filtrate was brought to pH 6 with 10N-hydrochloric acid (about 1 ml.) and filtered from a trace of slime which retarded crystallization. Deposition of crystals began and was complete after 2 days, affording cream-coloured (0·5-cm. crystals) *4-hydroxypteridine* (75%), unchanged at 350°. This gave only one spot in paper chromatography and was recrystallized from the minimum (33 parts) of boiling water (80% recovery). It was almost insoluble in boiling alcohol, amyl alcohol, xylene, anisole, nitrobenzene, pyridine, or acetonitrile, but crystallized well from formamide or diethylformamide. The colourless aqueous solution has a faintly bitter taste (cf. also Table I) (Found: C, 48·7; H, 2·7; N, 37·7. $C_6H_4ON_4$ requires C, 48·65; H, 2·7; N, 37·8%). This compound gave no colour with sulphuric acid or hydrochloric acid (10N.) and formed no picrate in aqueous solution. The sodium salt is soluble in 3 parts of water at 20°. Other chemical properties have been given in the introduction.

2-Aminopyrazine-3-carboxyamide (2 g.) and formic acid (4·5 ml.) were heated in an open vessel for 1 hour at 115° and then for 1 hour at 140°. The amide dissolved and was re-deposited, partly formylated, when the solvent evaporated. It was dried at 110° [Found: N, 35·9. $(C_6H_6O_2N_4)_2C_6H_4ON_4$ requires N, 36·0. Calc. for $C_6H_6O_2N_4$: N, 33·7%]. The degree of formylation was not increased by the use of anhydrous sodium formate or slowly distilling toluene. When heated to 225°, in a dry state, this partly formylated product gave 4-hydroxypteridine (III) in 43% yield; when it was boiled for 10 minutes with N-sodium ethoxide (alcoholic) a 60% yield was obtained, but refluxing it for 2 hours with acetic anhydride gave only 44% (these yields are based on the unformylated amine).

When 2-aminopyrazine-3-carboxyamide (1·38 g.) was refluxed with acetic anhydride (20 ml.) and formic acid (20 ml.) for 2 hours, 65% of 4-hydroxypteridine was obtained.

4-Mercaptopteridine.—2-Aminopyrazine-3-carboxythioamide (5·8 g.), ethyl orthoformate (100 ml.) and acetic anhydride (100 ml.) were heated under reflux at 145—150° for 2 hours. After refrigeration the yellow solid was filtered off and washed thoroughly with acetone. After being dried, it (5·2 g., 84%) was recrystallized from water (4 l.) containing charcoal (2 g.) with 70% recovery. *4-Mercaptopteridine* formed yellow crystals (decomp. 290°) from 800 pts. of boiling water, or from a very large volume of amyl alcohol or pyridine (Found: C, 44·0; H, 2·5; S, 19·5. $C_6H_4N_4S$ requires C, 43·9; H, 2·5; S, 19·5%).

Unsuccessful Attempts.—Failures to synthesize pteridines from pyrazine intermediates were: (i) 4-hydroxypteridine, by heating 2-aminopyrazine-3-carboxylic acid with formamide at 120° or 160°; (ii) 2 : 4-dihydroxypteridine, by refluxing 2-aminopyrazine-3-carboxyamide (II) with ethyl chloroformate, dioxan, and potassium carbonate, or by heating this amide or the corresponding acid with urea at 150° or 200°, or by dissolving the acid in aqueous potassium cyanate or by heating the acid with urethane; (iii) 4-aminopteridine, by heating 2-aminopyrazine-3-carboxyamide (or the corresponding nitrile) with formamide, even at 215°; (iv) pteridine, by heating 2-aminopyrazine-3-carboxyamide with aqueous formaldehyde in acid solution, or with aqueous hexamine, or with trioxymethylene and formic acid in alcohol, or by refluxing methyl 2-aminopyrazine-3-carboxylate with aqueous hexamine; (v) 4-hydroxy-2-mercaptopteridine, by refluxing 2-aminopyrazine-3-carboxyamide with carbon disulphide in pyridine. Sodium dithioformate did not react with (II).

Pteridines from Pyrimidine Intermediates.

Pteridine.—4 : 5-Diaminopyrimidine (16·2 g.), polyglyoxal (9·8 g., 1·1 equivs.), and alcohol (320 ml.) were refluxed for 30 minutes. The solvent was removed under reduced pressure and the residue extracted with benzene (3 × 100 ml.). The combined benzene extracts were boiled with two successive portions of charcoal, then concentrated to 100 ml. On cooling, pteridine crystallized out as yellow plates (10·2 g., dried in a vacuum at 20°). Further concentration to 10 ml. gave 2·0 g. more (total yield 63%). The m. p. was 137—138·5° (Found: C, 54·65; H, 3·1; N, 42·5. Calc. for $C_6H_4N_4$: C, 54·5; H, 3·0; N, 42·4%). Pteridine sublimes almost quantitatively at 125—130°/20 mm., giving denser yellow crystals, m. p. 139·5—140°, which appear to be another crystalline form because recrystallization from benzene, from 5 parts of alcohol (80% recovery), or from 300 parts of light petroleum (b. p. 60—80°; 80% recovery) gave the yellow plates, m. p. 138—138·5°. Pteridine is volatile in steam to only a small degree, and it was shown spectrographically that 0·1 g. yielded only 0·5 mg. in 15 ml. of distillate. The partition coefficient between chloroform and water is 1·98, whereas benzene and ether extract much less (coefficients: 0·21 and 0·05 respectively). The crystals provoke sneezing. Other physical properties of pteridine are given in Table I. No pteridine could be isolated when water replaced alcohol in the above synthesis.

4 : 5-Diaminopyrimidine (1·6 g.), glyoxal sodium bisulphite (4·5 g.; 1·1 equivs.), and water (14 ml.) were refluxed for 2 hours and then taken to dryness. The yellow residue was sublimed for 30 hours at 160—180°/20 mm. The reaction was completed only during this sublimation and gave a 15% yield of pteridine.

Pteridine N-Oxide.—To pteridine (0·5 g.) in chloroform (2 ml.) was added an ethereal solution of perphthalic acid (1·1 equivs.). The pale orange precipitate (1·35 g.) was dissolved in boiling methanol (330 ml.). From this solution, after treatment with charcoal, filtering, and cooling, a *N-oxide* crystallized (0·41 g., 72%). Recrystallization from methanol gave white crystals, decomp. *ca.* 350°, giving a single spot in paper chromatography (Found: C, 48·5; H, 2·55. $C_6H_4ON_4$ requires C, 48·65; H, 2·7%).

2-Aminopteridine.—To unpurified 2 : 4 : 5-triaminopyrimidine (20 g.) in water (140 ml.) was added a solution of glyoxal sodium bisulphite (50 g.) in warm water (350 ml.). The mixture was refluxed for 80 minutes, filtered by gravity, and refrigerated overnight. The precipitate (a sulphonic acid) was

filtered off, washed with a little ethanol, and dried at 110°. It was converted into 2-*aminopteridine* by 30 minutes' mechanical shaking at 20° with N-sodium hydroxide (250 ml.). The solid was filtered off, washed with water and alcohol, and dried at 105° (6·9 g.). A further 4·3 g. was obtained by treating the filtrate from the addition product with sodium hydroxide (10N.; 25 ml.) at 0° for 2 hours. The combined material (11·2 g.) was recrystallized 3 times from 110 parts of boiling water containing 0·2 part of charcoal. The crystals were washed with a little ethanol and dried at 105° for 10 minutes only. The final yield was 4·8 g. of yellow crystals, decomposing at about 275°. The substance was virtually insoluble in boiling alcohol, pyridine, or other common organic solvents (Found: C, 49·3; H, 3·15; N, 47·3. $C_6H_5N_5$ requires C, 49·0; H, 3·4; N, 47·6%).

2-*Dimethylaminopteridine.*—A warm solution of glyoxal sodium bisulphite (8 g.) in water (32 ml.) was added to a solution of crude 4 : 5-diamino-2-dimethylaminopyrimidine (3·2 g.) in water (16 ml.). After gently refluxing for 30 minutes, the solution was rapidly filtered from a little slime (heated funnel) and cooled to 0°. The bisulphite complex was filtered off, washed with a little cold water, and dissolved in 2·5N-sodium carbonate (45 ml.). The yellow solution was taken to dryness at 40° under reduced pressure. The residue was extracted with boiling ethanol (200 ml.), and the filtrate taken to dryness. The orange-coloured solid was dissolved in hot *cyclo*hexane (600 ml.), the solution filtered, and set aside at room temperature for 2 hours. The red flocculent precipitate was rejected and the solution concentrated to about 40 ml. and then cooled, and the yellow crystals were filtered off. Further concentration to 10 ml. gave another crop (total yield: 1·6 g., 43%). 2-*Dimethylaminopteridine* formed yellow fern-like crystals (m. p. 125—126°) from *cyclo*hexane. It was readily soluble in cold alcohol and benzene, also in boiling light petroleum and *cyclo*hexane (Found: C, 55·0; H, 5·2; N, 39·9. $C_8H_9N_5$ requires C, 54·85; H, 5·2; N, 40·0%).

4-*Aminopteridine.*—Unpurified 4 : 5 : 6-triaminopyrimidine (9·4 g.; m. p. 235—245°) in hot water (80 ml.) was added to a solution of glyoxal sodium bisulphite (22 g.) in hot water (160 ml.). The mixture was refluxed for 1 hour, cooled to 5°, and stirred with 10N-sodium hydroxide (15 ml.) to decompose the addition product. The mixture was then kept in ice for 30 minutes (no longer) and filtered. The precipitate of 4-*aminopteridine* was washed with a little cold water, then with alcohol, and dried at 110° (yield, 70%). It was twice recrystallized from boiling water (100 parts) containing charcoal (0·2 part) and dried at 110°, giving white plates (5 g.) decomposing at about 305° and almost insoluble in pyridine and other common organic solvents (Found: C, 49·0; H, 3·2; N, 47·5%).

2- *and* 4-*Acetamidopteridines.*—The aminopteridine (0·74 g.; 0·005M.) and acetic anhydride (5 ml.) were refluxed for 30 minutes and chilled overnight. The crystals were filtered off, washed with benzene, then with a little methanol, then shaken at 20° with 5N-ammonia for an hour, collected, and dried at 120°. 2-*Acetamidopteridine* formed pale buff-coloured crystals, m. p. 229—231° (decomp.) (70%), from 30 parts of boiling water; it was very soluble in boiling pyridine (Found: C, 51·0; H, 3·9; N, 36·4. $C_8H_7ON_5$ requires C, 50·8; H, 3·7; N, 37·0%). 4-*Acetamidopteridine* formed pale buff-coloured crystals, m. p. 191—192°, from 2 parts of boiling water or 30 parts of toluene (Found: C, 51·2; H, 3·6; N, 36·1%).

2-*Hydroxypteridine.*—Glyoxal (28 g. of the commercial 50% aqueous solution) was added in one portion to a solution of 4 : 5-diamino-2-hydroxypyrimidine (14 g.; Johns, *Amer. Chem. J.*, 1911, **45**, 79) in boiling water (200 ml.). After 15 minutes' refluxing, the suspension was cooled and refrigerated overnight. The solid was filtered off and, without being dried, recrystallized from the minimal amount of water (*ca.* 750 ml.), containing charcoal (3 g.), and filtered through a heated funnel. The pale orange filtrate at once deposited cream-coloured needles (14·6 g., 80%). After two similar recrystallizations from 50 parts of water, 10 g. of white needles of 2-*hydroxypteridine monohydrate* (decomp. 240°) were obtained. It is almost insoluble in all common organic solvents (Found, for material dried at 120°/0·1 mm. for 30 minutes: C, 43·55; H, 3·65; N, 33·8. $C_6H_4ON_4,H_2O$ requires C, 43·4; H, 3·65; N, 33·75%). Boiling for 30 minutes with 0·1N(or for 1 minute with 5N)-sodium hydroxide or -hydrochloric acid produces a blue colour.

2-Hydroxypteridine was also prepared by the hydrolysis of 2-chloropteridine (0·2 g.) in water (7 ml.) at 100°. The pH rapidly decreased and on reaching *ca.* 1—2 was raised with 5% sodium hydrogen carbonate solution to *ca.* 6. This adjustment was continued until no further fall occurred (½ hour), by which time 95% of the theoretical amount of alkali had been added. The orange solution, boiled with charcoal, filtered, and refrigerated, gave 2-hydroxypteridine monohydrate (0·1 g.).

4-*Hydroxypteridine.*—4 : 5-Diamino-6-hydroxypyrimidine (13 g.) was added to a solution of glyoxal sodium bisulphite (31·2 g.) in warm water (390 ml.), and the whole refluxed for 1 hour. The solution was cooled to 80° and 10N-hydrochloric acid (25 ml.) added. The solution was boiled vigorously for 10 minutes to expel sulphur dioxide, adjusted to pH 3—4 with 2·5N-sodium hydroxide (*ca.* 20 ml.), cooled to 20°, filtered from a dark slime, and then refrigerated for a day. The buff-coloured crystals were dried at 110° and recrystallized once from 30 parts of water containing 0·4 part of charcoal (yield: 10·4 g., 68%) (Found: C, 49·1; H, 2·7; N, 38·0. $C_6H_4ON_4$ requires C, 48·65; H, 2·7; N, 37·8%). Traces of coloured impurity were removed by filtering off the first few crystals which were found to adsorb it strongly. The properties have been given above.

4-Hydroxypteridine was also prepared from 4-aminopteridine (5 g.) dissolved in boiling water (450 ml.). Sodium hydroxide (50 ml.; 10N.) was added to initiate the hydrolysis and after 5 minutes' refluxing the solution was brought to pH 4—5 with 10N-hydrochloric acid and refrigerated for a day. 4-*Hydroxypteridine* was obtained as fine white needles in 80% yield (including a second crop got by concentration to 150 ml.). After one recrystallization, the material was chromatographically and spectrographically pure (Found: C, 48·55; H, 2·65; N, 37·9%).

4-*Hydroxy*-6 : 7-*dimethylpteridine.*—Commercial diacetyl was fractionated through a 60-cm. Vigreux column fitted with a total condensation head. A reflux ratio of 7 : 1 was maintained and the fraction boiling at 89·5—90° collected. Pure diacetyl (9 ml.) was added, with shaking, to a solution of 4 : 5-di-

amino-6-hydroxypyrimidine (12·5 g.) in water (100 ml.) at 75°. After being heated on the water-bath for 20 minutes the mixture was refrigerated overnight. The precipitate was filtered off, washed with cold water (20 ml.), and dried at 120° (14·3 g., 81%). The product was recrystallized from 100 parts of boiling water with carbon (3 g.), giving 12·3 g. of white needles, 1 cm. long, of *4-hydroxy-6 : 7-dimethylpteridine* (decomp. 355—360°) (Found : C, 54·6; H, 4·35; N, 31·6. $C_8H_8ON_4$ requires C, 54·55; H, 4·55; N, 31·8%). Unlike 4-hydroxypteridine it dissolved in boiling amyl alcohol.

2 : 4-*Dihydroxypteridine*.—Glyoxal sodium bisulphite (70 g.) in warm water (750 ml.) was added to a suspension of 4 : 5-diamino-2 : 6-dihydroxypyrimidine sulphate (50 g.; Bogert and Davidson, *J. Amer. Chem. Soc.*, 1933, **55**, 1667) in 1·2N-hydrochloric acid (570 ml.). The mixture was refluxed for an hour, cooled to 10°, and filtered by gravity. The filtrate, refrigerated for 3 days, deposited brown crystals (30 g.) which were boiled with water (1350 ml.) containing charcoal (15 g.) for 5 minutes and filtered. The filtrate was boiled with chromatographic alumina (15 g.) and re-filtered. The second filtrate was allowed to crystallize overnight and the crystals were treated three times more in the same way, using proportional amounts of adsorbents. Perfectly white crystals, 2 mm. long, decomp. 335—338°, giving a colourless saturated solution in boiling water, were obtained (Found, for material dried at 140° : C, 44·05; H, 2·45; N, 34·9. Calc. for $C_6H_4O_2N_4$: C, 43·9; H, 2·45; N, 34·2%). This highly purified substance is much less fluorescent than the crude material which is known as "lumazine" (Kuhn and Cook, *loc. cit.*). An easier, and almost as satisfactory, purification for small amounts was percolation of 100 ml. of a 1% solution of the ammonium salt of 2 : 4-dihydroxypteridine through a column (10 × 3 cm.) of chromatographic alumina, followed by elution with water and acidification of the eluate.

By isolating their product in the presence of ammonia, some previous workers (*e.g.*, Weijlard, Tishler, and Erickson, *loc. cit.*) have unwittingly obtained the sparingly soluble ammonium salt, ammonia being lost on drying for analysis.

2-*Chloropteridine*.—4 : 5-Diamino-2-chloropyrimidine (3·5 g.) and dry polyglyoxal (2 g.) were refluxed in dry methanol (35 ml.) for 10 minutes. The solution was evaporated *in vacuo* at 30° and the residual thick red gum was extracted first with light petroleum (150 ml.; b. p. 60—80°) and then with light petroleum (150 ml.; b. p. 80—100°). After refrigeration, the extract yielded 1·0 g. (25%) of yellow crystals, m. p. 98—101°. Several recrystallizations from light petroleum (250 parts; b. p. 60—80°) gave slightly yellow needles of *2-chloropteridine*, m. p. 106—107° (decomp.) (Found : N, 33·65; Cl, 21·1. $C_6H_3N_4Cl$ requires N, 33·65; Cl, 21·3%). This is readily hydrolysed to 2-hydroxypteridine in mildly acid solution, but stronger acids disrupt the ring with the production of a violet colour.

2-Mercaptopteridine was synthesized according to Elion and Hitchings (*loc. cit.*); 2-amino-4-hydroxypteridine according to Cain, Mallette, and Taylor (*J. Amer. Chem. Soc.*, 1946, **68**, 1996); leucopterin according to Totter (*J. Biol. Chem.*, 1944, **154**, 105). Xanthopterin was synthesized according to Elion, Light, and Hitchings (*J. Amer. Chem. Soc.*, 1949, **71**, 741) and further purified through its barium salt (Schöpf and Becker, *Annalen*, 1933, **507**, 266) (Found, for material dried at 20°/20 mm. over calcium chloride : C, 36·3; H, 3·4; N, 35·4. Calc. for $C_6H_5O_3N_5,H_2O$: C, 36·5; H, 3·6; N, 35·5%).

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Department of Medical Chemistry,
The Australian National University,
183 Euston Road, London, N.W.1.

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104. *Antituberculous Compounds. Part VII. Some Further N-Substituted Amidines and Analogues.*

By P. T. Charlton, G. K. Maliphant, P. Oxley, and D. A. Peak.

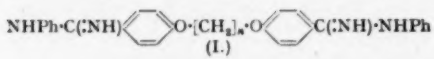
In order to investigate the relation between structure and activity against *Mycobacterium tuberculosis* a number of *N*-substituted aromatic, alicyclic, and aliphatic amidines have been prepared in which the *N*-substituents are in most cases aryl groups of varied type, modified in some compounds as *NN'*-cyclised structures. A few related unsubstituted amidines, dihydroglyoxalines, and *N*-alkyl- or *N-cyclo*alkyl-amidines have also been prepared.

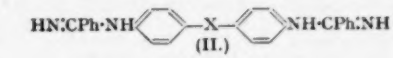
The activity *in vitro* against *Mycobacterium tuberculosis* of di-(*p*-*N*-arylamidinophenoxy)alkanes (Part II; *J.*, 1949, 2683) and *p*-alkoxy-*N*-arylbenzamidines (Part III; *J.*, 1949, 3043) prompted us to examine a wider range of *N*-substituted amidines in the hope of gaining further insight into the relative importance of the *N*-substituent and of the amidine moiety. Except in a few of the compounds prepared, the *N*-aryl substituent was retained throughout, though of varied type and often considerably modified as an *NN'*-cyclised structure. In a large proportion of

the compounds, however, the aryl radical of the amidine moiety was replaced by an alicyclic or an aliphatic radical, a change frequently resulting in compounds of high activity *in vitro*.

The compounds prepared are enumerated in the accompanying table, together with yields and methods of preparation. The methods were for the most part those developed in these laboratories for the preparation of amidines (Oxley and Short, *J.*, 1946, 147; 1947, 497; 1949, 449; Oxley, Partridge, and Short, *J.*, 1947, 1110) and presented no novel features. In a few cases other methods had to be adopted. These are noted in the discussion below in which the number in parentheses following the name of a compound refers to the number of the compound in the table. Activities *in vitro* are also recorded in the table. Compounds were tested as aqueous solutions of their salts, free bases being in most cases dissolved in an equivalent of aqueous lactic acid. Derivatives unsuitable for testing, such as picrates and reineckates, were first converted into solutions of the base hydrochlorides by standard procedures.

The parent compound *N*-phenylbenzamidine (1) had little activity. The symmetrically substituted *NN'*-diphenylbenzamidine (2) had an even lower activity in agreement with the low activities of the two *NN'*-diphenylbenzamidines described in Part III (*loc. cit.*). The unsymmetrically substituted *NN*-diphenylbenzamidine (3) gave appreciably higher activity and this effect will be referred to again later. A cursory examination of other *N*-phenylbenzamidines (compounds 4—9), substituted in one or both *p*-positions, indicated nothing of promise. *N*-Alkyl substitution as in *N*-methyl-, *N*-octyl-, and *N*-2-diethylaminoethyl-*N*-phenylbenzamidines (10, 11, and 12) gave moderate activity only in the case of the octyl compound.


(I.)


(II.)

An interesting alternation of activity in the odd and even members of the di-(*p*-*N*-phenylamidinophenoxy)alkane series (I; $n = 2$—6) was noted in Part II (*loc. cit.*). No such alternation was shown in a series of di-(*p*-benzimidamidophenoxy)alkanes (20, 21, and 22) (II; X = O·[CH$_2$]$_n$·O where $n = 2$, 3, and 4, respectively) in which nitrogen atoms of two benzamidine residues are linked by the diphenoxyalkane group. All three compounds had comparable high activity, as had also the analogous di-(*p*-benzimidamidophenyl) ether (19) (II; X = O).

In contrast to the low activities of *N*-phenylbenzamidine (1) and *p*-methanesulphonyl-*N*-phenylbenzamidine (6), the corresponding *N*-2-diphenylyl compounds (13 and 14) showed activity of a high order. This powerful activating effect of the 2-diphenylyl group has already been noted in Part III (*loc. cit.*) and is a feature of other 2-diphenylyl derivatives described in the present communication. The corresponding *N*-3-diphenylyl- and *N*-4-diphenylyl-benzamidines (15 and 16) were less active in the absence but of the same order in the presence of serum. The preparation of a series of *N*-4-diphenylyl-amidines, including the latter compound, for antituberculous test has recently been described by Bauer and Cymerman (*J.*, 1950, 1826) who make no reference to the high activity of the analogous *N*-2-diphenylyl compounds here described although the latter author was aware of our results. An increment of activity of a somewhat lower order, especially in the presence of serum, was produced by *N*-1-naphthyl and *N*-2-naphthyl substitution (compounds 17 and 18).

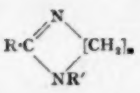
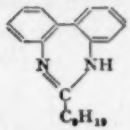
2-Phenylbenziminazole (23), which may be regarded as a cyclised form of *N*-phenylbenzamidine, had moderate activity but a series of 2-phenylbenziminazoles (24—33) substituted in the *p*-position of the 2-phenyl substituent or in the benziminazole nucleus proved of no interest. A number of these compounds were more conveniently prepared by oxidation of a mixture of the appropriate *o*-phenylenediamine and arylaldehyde with copper acetate (Wiedenhagen, *Ber.*, 1936, 69, 2263) than by the fusion method.

The series of *N*-arylamidino*cyclo*-hexanes and -hexenes (compounds 34—43) presented several points of interest. With the noteworthy exception of 1-*N*-2'-diphenylylamidino*cyclo*hexene (43), replacement of the aromatic nucleus of the benzamidine by *cyclo*hexyl and *cyclo*hexenyl groups if anything enhanced the activity. On the other hand, replacement of the *N*-aryl group by an *N*-*cyclo*hexyl group, as in 1-*N*-*cyclo*hexylamidino*cyclo*hexene (42), led to a compound of low activity. In contrast to the deactivating action of a *p*-chloro-atom in the *N*-phenyl substituent of 1 : 3-di-(*p*-*N*-*p'*-chlorophenylamidinophenoxy)propane (Part II; *loc. cit.*) and its neutral action in *p*-butoxy-*N*-*p'*-chlorophenylbenzamidine (Part III; *loc. cit.*), similar substitution, though not *o*-chloro-substitution, of 1-*N*-phenylamidino*cyclo*hexene appreciably increased the activity (compounds 40 and 41).

The benzamidine moiety may be further modified without loss of activity. Higher members of the series of *N*-phenylamidinoalkanes (compounds 44—50) exhibited high activity in the

absence of serum but both these and the less active lower members were considerably deactivated by serum. Of three analogous *N*-2-diphenylyl compounds, only 1-*N*-2′-diphenylylamidinononane (53) and, to a lesser extent, the heptane analogue (51), showed the expected exaltation of activity. In contrast the corresponding octane analogue (52) was of relatively low activity. All three compounds were, however, reduced to comparable levels of activity by serum.

The analogous series of 1-*N*-2′-naphthylamidinoalkanes (54—62) showed only a uniformly moderate activity in serum comparable with that of the *N*-phenyl analogues. 1-*N*-1′-Naphthylamidinononane (63), the only member which was prepared in the corresponding 1-naphthyl series, was considerably more active than the 2-naphthyl analogue (62). This is the reverse of

(III.)  (IV.) 

the observed order of activity of the two naphthylamines themselves (Bloch, Lehr, and Erlenmeyer, *Helv. Chim. Acta*, 1945, **28**, 1406; Doub and Youmans, *Amer. Rev. Tuberc.*, 1950, **61**, 407).

In view of the general high level of activity of the amidinononanes, further examples of compounds containing this grouping were prepared. 1-*NN*-Diphenylamidinononane (64) was of unexpectedly low activity in view of the positive effect of *NN*-diphenyl substitution in benzamidine (cf. compound 3) and was, in fact, no more active than the unsubstituted 1-amidinononane (65).

In 4 : 5-dihydro-2-nonylglyoxaline (66) (III; R = C_9H_{19}, R′ = H, n = 2) a compound of high activity in both the absence and the presence of serum was encountered, but the homologous tetrahydropyrimidine (67) (III; R = C_9H_{19}, R′ = H, n = 3) was feebly active in comparison. Introduction of an *N*-phenyl group into the dihydroglyoxaline (66) gave a compound (68) (III; R = C_9H_{19}, R′ = Ph, n = 2) also of high activity but more susceptible to deactivation by serum. 2-Nonylbenziminazole (69) was about as active as its uncyclised analogue *N*-phenylamidinononane (50), but 2-nonyl-1 : 3-diaza-4 : 5 : 6 : 7-dibenz*cyclo*heptatriene (70) (IV) much less so than its analogue, 1-*N*-(2-diphenylyl)amidinononane (53).

A further example of the potent effect of the dihydroglyoxaline group was furnished by the high activity of 2-heptadecyl-4 : 5-dihydroglyoxaline (72) (III; R = $C_{17}H_{35}$, R′ = H, n = 2) in comparison with the virtual inactivity of 1-amidinoheptadecane (71).

Finally, a few *N*-mono- and -di-alkylated acetamidines were prepared which support the indication observed in the case of the *NN*′- and *NN*-diphenylbenzamidines (2 and 3) that unsymmetrical rather than symmetrical substitution of the amidine group favours activity. Purely aliphatic amidines, mainly *N*-unsubstituted or *N*-monoalkyl-α-alkylated acetamidines, have previously been found active against *M. tuberculosis* (Newbery and Webster, *J.*, 1947, 738). *N*-Octyl-, *NN*-dioctyl-, and *N*-hexadecyl-acetamidines (73, 75, and 76) were prepared by the Pinner route. The usual procedure of treating the imino-ether hydrochloride with the base gave complex mixtures from which it was not possible to isolate the required amidines. However, reaction of a two-fold excess of the base with free acetimido-ether (cf. Ashley *et al.*, *J.*, 1942, 107) for several days (as judged by the rapidity of development of an alkaline reaction to Titan-yellow indicator) provided a practicable method. Attempted preparation of *N*-octylacetamidine from methyl cyanide and octylamine by the aluminium chloride method (Oxley, Partridge, and Short, *loc. cit.*) afforded none of the expected product, but *NN*′-dioctylacetamidine (74) in poor yield. Peak activity was again associated with the unsymmetrically disubstituted *NN*-dioctylacetamidine, both the isomeric *NN*′-dioctyl- and *N*-hexadecyl-acetamidines being considerably less active. The complexity of the factors involving activity is, however, illustrated by the complete reversal of relative activities of the isomeric pair, *N*-octylacetamidine (73) and 1-amidinononane (65), in comparison with the analogous isomeric pair, *N*-heptadecylacetamidine (76) and 1-amidinoheptadecane (71).

Tests *in vivo* on certain of these compounds, selected for favourable activity and toxicity, have already been reported (Croshaw and Dickinson, *Brit. J. Pharm.*, 1950, **5**, 178). The results were uniformly negative.

Experimental

Preparation of Amidines.—The following general methods were used as indicated in the table. The yields recorded in the table refer to the pure compound first isolated.

Compound.	Activity: ‡ in absence of serum.	Activity: ‡ in presence of 10% serum.	Method.	Yield, %.	Derivative.	Solvent.†	Crystal form.	M. p.	Formula.	N, %. Found.	N, %. Reqd.
Benzamidines.											
(1) *N*-Phenyl-	1	—	—	—	—	—	—	—	—	—	—
(2) *NN'*-Diphenyl-	<1 (1)	—	—	—	—	—	—	—	—	—	—
(3) *NN*-Diphenyl-	5 (10)	—	—	—	—	—	—	—	—	—	—
(4) 3 : 4-Dimethoxy-*N*-phenyl-	1	—	—	—	—	—	—	—	—	—	—
(5) *N*-Phenyl-*p*-sulphamyl-	1	—	—	—	—	—	—	—	—	—	—
(6) *p*-Methanesulphonyl-*N*-phenyl-	1	—	—	—	—	—	—	—	—	—	—
(7) *N*-*p*-Methoxyphenyl-	10	—	—	—	—	—	—	—	—	—	—
(8) N-(*p-Methanesulphonyl-phenyl*)-	1	—	D	92	—	Aq. EtOH	Needles	177·5—178°	$C_{14}H_{14}O_2N_2S$	10·1	10·2
					Hydrochloride	EtOH	Cubes	263—265 *	$C_{14}H_{15}O_2N_2ClS$	8·9	9·0
					Picrate	MeOH	Leaflets	137—138	$C_{20}H_{17}O_9N_5S,H_2O$	13·35	13·35
(9) p-*Methanesulphonyl-N*-(*p-methanesulphonyl-phenyl*)-	<1	—	A	60	—	Aq. ethoxy-ethanol	Needles	286—287 *	$C_{15}H_{16}O_4N_2S_2$	7·95	7·95
					Hydrochloride	H_2O	Rosettes, fine needles	270—271 *	$C_{15}H_{17}O_4N_2ClS_2$	7·1	7·2
(10) *N*-Methyl-*N*-phenyl-	1	—	—	—	—	—	—	—	—	—	—
(11) *N*-Octyl-*N*-phenyl-	—	10	D	85	*Reineckate*	H_2O	—	116	$C_{23}H_{39}N_6S_4Cr$	17·6	17·9
(12) *N*-2-Diethylamino-ethyl-*N*-phenyl-	—	1	D	16	*Dipicrate*	MeOH	Needles	109	$C_{31}H_{31}O_{14}N_9$	16·4	16·7
(13) *N*-2-Diphenylyl-	100 (500)	10 (100)	—	—	—	—	—	—	—	—	—
(14) *N*-2-Diphenylyl-*p*-methanesulphonyl-	100	—	—	—	—	—	—	—	—	—	—
(15) N-3-*Diphenylyl*-	50—100	10—50	A	54	—	80% EtOH	Prisms	135—136	$C_{19}H_{16}N_2$	10·15	10·3
(16) *N*-4-Diphenylyl-	50	50	A	57	—	EtOH	Needles	182	$C_{19}H_{16}N_2$	10·3	10·3
(17) *N*-1-Naphthyl-	100	10	A	77	—	80% EtOH	Needles	145	$C_{17}H_{14}N_2$	11·3	11·4
(18) N-2-*Naphthyl*-	10—50	10—50	A	77	—	80% EtOH	Pale yellow plates	123	$C_{17}H_{14}N_2$	11·5	11·4
(19) Di-(*p*-benzimidamido-phenyl) ether	100	10—50	A	40	*Dihydrochloride*	H_2O	Plates	206	$C_{26}H_{24}ON_4Cl_2$	11·9	11·7
(20) 1 : 2-Di-(*p*-benzimid-amidophenoxy)ethane	100	50	A	41	*Dihydrochloride*	H_2O	Plates	280 *	$C_{28}H_{28}O_2N_4Cl_2$	11·0	10·7
(21) 1 : 3-Di-(*p*-benzimid-amidophenoxy)propane	—	50	A	59	*Dihydrochloride*	H_2O	Plates	163—165	$C_{29}H_{30}O_2N_4Cl_2$	10·05	10·4
(22) 1 : 4-Di-(*p*-benzimid-amidophenoxy)butane	—	10—50	A	33	*Dihydrochloride*	H_2O	Small prisms	179—180	$C_{30}H_{32}O_2N_4Cl_2$	10·2	10·2
Benziminazoles.											
(23) 2-Phenyl-	10	1 (10)	C	54	—	—	—	—	—	—	—
(24) 2-*p*-Tolyl-	—	1	C	47	—	60% EtOH	Prisms	269	—	—	—
					Hydrochloride	EtOH	Needles	275	$C_{14}H_{12}N_2Cl$	11·4	11·4

Benziminazoles (contd.)											
(25) 2-p-*Hydroxyphenyl-*	—	5—10	C	60	—	60% EtOH	Prisms	279	$C_{13}H_{10}ON_2$	13·1	13·1
					Hydrochloride	EtOH	Prisms	346	$C_{13}H_{11}ON_2Cl$	11·15	11·4
(26) 2-*p*-Methoxyphenyl-	—	1	E	56	—	Aq. MeOH	Needles	227	$C_{14}H_{12}ON_2$	13·1	12·5
					Hydrochloride	EtOH	Needles	267	$C_{14}H_{13}ON_2Cl$	10·6	10·75
(27) 2-*p*-Nitrophenyl-	—	1	E	51	*Sesquihydrate*	80% EtOH	Minute needles	298—299	$C_{13}H_9O_2N_3,1{\cdot}5H_2O$	15·9	15·8
(28) 2-*p*-Aminophenyl-	—	5	F	90	—	—	—	239	—	—	—
					Dihydrochloride	50% EtOH –aq. HCl	Prisms	351	$C_{13}H_{13}N_3Cl_2$	15·2	14·9
(29) 2-p-*Sulphamylphenyl-*	—	1	A	44	—	Aq. EtOH	Prisms	321	$C_{13}H_{11}O_2N_3S$	15·2	15·4
					Hydrochloride	EtOH	Prisms	335	$C_{13}H_{12}O_2N_3ClS,H_2O$	12·6	12·8
(30) 2-α-Furyl-	—	<1 (10)	E	60	—	EtOH	Needles	284	$C_{11}H_8ON_2$	15·4	15·2
					Hydrochloride	50% EtOH	Needles	299	$C_{11}H_9ON_2Cl,H_2O$	11·8	11·8
(31) 4-Nitro-2-phenyl-	—	—	E	44·5	*Hydrochloride*	EtOH	Prisms	252 *	$C_{13}H_{10}O_2N_3Cl$	15·5	15·3
(32) 4-Amino-2-phenyl-	—	1	F	39	*Dihydrochloride*	80% EtOH	Prisms	264	$C_{13}H_{13}N_3Cl_2$	15·1	14·9
(33) 5-Amino-2-phenyl-	—	<1	F	81	Dihydrochloride	Aq. EtOH–HCl	Prisms	322	$C_{13}H_{13}N_3Cl_2$	15·0	14·9
Amidino*cyclo*hexanes.											
(34) *N*-Phenyl-	5 (10)	—	—	—	—	—	—	—	—	—	—
(35) N-p-*Butoxyphenyl-*	100	10—50	B	52	—	Petrol	Plates	90	$C_{17}H_{28}ON_2$	10·1	10·2
					Toluene-p-sulphonate	PrⁱOH	Plates	168·5—169	$C_{24}H_{34}O_4N_2S$	6·4	6·3
1-***Amidino*cyclo*hexenes.***											
(36) *N*-Phenyl-	5 (10)	—	—	—	—	—	—	—	—	—	—
(37) *N*-*p*-Methoxyphenyl-	10	—	A	57	*Benzene-sulphonate*	H_2O	Prisms	171	$C_{20}H_{24}O_4N_2S$	7·3	7·2
(38) N-p-*Ethoxyphenyl-*	50	—	B	62	—	Petrol	Indef.	95	$C_{18}H_{30}ON_2$	11·4	11·5
					Picrate	PrⁱOH	Indef.	136	$C_{24}H_{33}O_8N_5$	15·0	14·8
(39) N-p-*Butoxyphenyl-*	500 (10,000)	100	B	65	—	Petrol	Prisms	69	$C_{17}H_{26}ON_2$	10·5	10·3
					Hydrochloride	H_2O	Plates	143	$C_{17}H_{25}ON_2Cl$	9·1	9·1
(40) N-p-*Chlorophenyl-*	50	10—50	A	92	—	C_6H_6	Prisms	131	$C_{13}H_{11}N_2Cl$	11·9	11·9
					Picrate	PrⁱOH	Indef.	193	$C_{19}H_{14}O_7N_5Cl$	15·2	15·1
(41) N-o-*Chlorophenyl-*	1—5	—	A	41	—	Petrol	Prisms	77	$C_{13}H_{11}N_2Cl$	11·9	11·9
					Picrate	PrⁱOH	Indef.	185	$C_{19}H_{14}O_7N_5Cl$	15·1	15·1
(42) *N*-*cyclo*Hexyl-	1	—	D	91	*Hydrochloride*	H_2O	Indef.	291 *	$C_{19}H_{23}N_2Cl$	11·6	11·55
(43) *N*-2'-Diphenylyl-	10	—	—	—	—	—	—	—	—	—	—
1-N-***Phenylamidino*-*alkanes.***											
(44) *-propane*	10	1—5	A	66	—	Petrol	Rhombs	67	$C_{10}H_{14}N_2$	17·2	17·3
					Picrate	PrOH	Rhombic plates	142—142·5	$C_{16}H_{17}O_7N_5$	18·1	17·9
(45) *-butane*	5—10	<1 (10)	A	69	—	Petrol	Flat needles	59	$C_{11}H_{16}N_2$	16·1	15·9
					Picrate	PrⁱOH	Rhombic prisms	139·5—140	$C_{17}H_{19}O_7N_5$	17·3	17·3
(46) *-pentane*	10—100	5—10	A	60	—	Petrol	Flat needles	58	$C_{12}H_{18}N_2$	14·7	14·7
					Picrate	PrⁱOH	Indef.	97	$C_{18}H_{21}O_7N_5$	16·7	16·7

Compound.	Activity: ‡ in absence of serum.	Activity: ‡ in presence of 10% serum.	Method.	Yield, %.	Derivative.	Solvent.†	Crystal form.	M. p.	Formula.	N, %. Found.	N, %. Reqd.
1-*N*-*Phenylamidino-alkanes* (contd.)											
(47) -*heptane*	500	10	A	80	—	Petrol	Long needles	54	$C_{14}H_{22}N_2$	12·6	12·8
					Picrate	Et_2O	Plates	92—93	$C_{20}H_{25}O_7N_5$	15·9	15·7
					Benzene-sulphonate	$COMe_2$	Plates	96	$C_{20}H_{28}O_3N_2S$	7·6	7·45
(48) -*octane*	100—500	10—50	A	64	—	Petrol	Flat needles	61	$C_{15}H_{24}N_2$	12·0	12·1
					Picrate	Pr^iOH	Small plates	93	$C_{21}H_{26}O_7N_5$	14·7 14·7	15·2
					Benzene-sulphonate	$COMe_2$	Plates	102	$C_{21}H_{30}O_3N_2S$	7·2	7·2
(49) -*nonane*	500	10	A	62	—	Petrol	Needles	70	$C_{16}H_{26}N_2$	11·25	11·4
(50) 1-*N*-*p*-Tolylamidino-butane	50 (100)	—	—	—	—	—	—	—	—	—	—
1-N-2′-*Diphenylylamidino-alkanes.*											
(51) -heptane	500—1000	100	—	—	—	—	—	—	—	—	—
(52) -*octane*	100	50	A	37	—	Petrol (40—60°) or aq. $COMe_2$	Needles	97·5—98	$C_{21}H_{28}N_2$	9·15	9·1
(53) -nonane	5000	50—500	—	—	—	—	—	—	—	—	—
1-N-2′-*Naphthylamidino-alkanes.*											
(54) -*methane*	—	10	A	68	—	Petrol	Prisms	82	$C_{12}H_{12}N_2$	15·5	15·2
					Benzene-sulphonate	Pr^iOH	Prisms	142	$C_{18}H_{18}O_3N_2S$	7·9	8·2
(55) -*ethane*	—	10	A	50·5	—	Petrol	Long prisms	79—80	$C_{13}H_{14}N_2$	14·1	14·1
(56) -*propane*	—	10	A	86	—	Petrol	Prisms	64—66	$C_{14}H_{16}N_2$	13·3	13·2
					Benzene-sulphonate	Aq. EtOH	Plates	133—134	$C_{20}H_{22}O_3N_2S$	7·5	7·6
(57) -*butane*	—	10	A	22	—	Petrol	Plates	62—64	$C_{15}H_{18}N_2$	12·4	12·4
(58) -*pentane*	—	10	A	35	—	Petrol	Plates	72—74	$C_{16}H_{20}N_2$	11·9	11·7
(59) -*hexane*	10	10	B	79	—	Petrol	Prisms	59	$C_{17}H_{22}N_2$	10·8	11·0
					Toluene-p-sulphonate	Aq. EtOH	Plates	138	$C_{24}H_{30}O_3N_2S$	6·7	6·6
(60) -*heptane*	—	10—50	B	69	—	Et_2O–petrol	Prisms	61	$C_{18}H_{24}N_2$	10·45	10·45
					Toluene-p-sulphonate	Aq. EtOH	Plates	151	$C_{25}H_{32}O_3N_2S$	6·25	6·4
(61) -*octane*	—	10	B	83	—	Petrol	Plates	74	$C_{19}H_{26}N_2$	9·75	9·9
					Toluene-p-sulphonate	Aq. EtOH	Plates	156	$C_{26}H_{34}O_3N_2S$	6·4	6·2
(62) -*nonane*	—	5	B	67	—	Petrol	Plates	75	$C_{20}H_{28}N_2$	9·7	9·5
					Toluene-p-sulphonate	Pr^iOH	Plates	158	$C_{27}H_{36}O_3N_2S$	6·05	6·0

Various.											
(63) 1-*N*-1′-Naphthyl-amidinononane	100	100	A	45	*Benzene-sulphonate*	CCl_4	Plates	70—72	$C_{26}H_{34}O_2N_2S$	6·15	6·15
(64) 1-*NN*-Diphenyl-amidinononane	10	1	D	63	*Picrate*	EtOH	Prisms	118·5	$C_{28}H_{32}O_7N_5$	12·6	12·7
					Picrolonate	EtOH	Rods	142—143	$C_{32}H_{38}O_5N_6$	14·2	14·3
(65) 1-Amidinononane	10	—	A	41	*Benzene-sulphonate*	80% EtOH	Plates	92—94	$C_{16}H_{26}O_2N_2S$	8·5	8·5
(66) 4 : 5-*Dihydro*-2-*nonylglyoxaline*	100—500 (1000)	100 (500)	C	60	—	Et_2O–petrol	Plates	74—76	$C_{12}H_{24}N_2$	14·3	14·3
(67) 3 : 4 : 5 : 6-Tetrahydro-2-nonylpyrimidine	—	10	C	90	*Reineckate*	$COMe_2$–$CHCl_3$	Feathery needles	147—148	$C_{17}H_{32}N_6S_4Cr$	21·3	21·2
(68) 4 : 5-*Dihydro*-2-*nonyl*-1-*phenylglyoxaline*	1000	10 (500)	C	18	—	—	—	—	$C_{18}H_{28}N_2$	10·5	10·3
(69) 2-*Nonylbenziminazole*	50	5—10	C	52	—	Aq. EtOH	Indef.	124—126	$C_{16}H_{24}N_2$	11·5	11·5
(70) 2-*Nonyl*-1 : 3-*diaza*-4 : 5 : 6 : 7-*dibenzo*-cyclo*heptatriene*	10	5—10	C	45	—	Petrol	Indef.	73—75	$C_{22}H_{26}N_2$	9·1	8·75
(71) 1-Amidinoheptadecane	<1	—	A	26	*Benzene-sulphonate*	MeOH	Indef.	92—95	$C_{24}H_{44}O_3N_2S$	6·1	6·4
(72) 2-*Heptadecyl*-4 : 5-*dihydroglyoxaline*	500—1000	100	C	73	—	$COMe_2$	Plates	94	$C_{20}H_{40}N_2$	9·2	9·1
Acetamidines.											
(73) *N*-Octyl-	<1	—	G	67	*Reineckate*	H_2O	Indef.	137	$C_{16}H_{39}N_6S_4Cr$	23·2	23·0
(74) *NN*′-Dioctyl	7·5	—	D	8	*Hydrochloride*	EtOH–$COMe_2$	Indef.	265—268	$C_{16}H_{35}N_2Cl$	9·0	8·8
(75) *NN*-Dioctyl-	50	—	G	85	*Picrate*	Et_2O	Prisms	89	$C_{34}H_{41}O_7N_5$	13·65	13·7
(76) N-*Hexadecyl*-	10	—	G	13	—	Et_2O	Indef.	71·5	$C_{16}H_{35}N_2$	10·3	10·0
					Picrate	Et_2O	Minute needles	114	$C_{24}H_{38}O_7N_5$	13·75	13·7

* With decomposition. † Petrol = light petroleum (b. p. 60—80°).

‡ Dilution (in thousands) at which complete inhibition of the growth of *M. tuberculosis* (human virulent strain) was maintained for 4 weeks in modified Long's medium (by the floating pellicle method) (Croshaw and Dickinson, *loc. cit.*). Figures in parentheses represent dilutions at which partial inhibition occurred. Under the same conditions of test 4-aminosalicylic acid gave a value of 10 in the absence of serum.

(1), (2), and (3) Oxley and Short, *J.*, 1946, 147. (4), (5), (6), and (7) Oxley and Short, *J.*, 1949, 449. (8) and (9) Preparations by Dr. M. W. Partridge. (10) Oxley, Partridge, and Short, *loc. cit.* (11) Prepared by precipitation of the crude hydrochloride with ammonium reineckate. (13) and (14) Cymerman and Short, *J.*, 1949, 703. (17) Bernthsen and Trompetter (*Ber.*, 1878, **11**, 1757) give m. p. 141°. (23) Cf. Holljes and Wagner, *J. Org. Chem.*, 1944, **9**, 31. (24) Brücker (*Annalen*, 1880, **205**, 118) and Hübner (*ibid.*, 1881, **210**, 329) record m. p. 268°; Wuyts and Vaerenbergh (*Bull. Soc. chim. Belg.*, 1939, **48**, 329), m. p. 265°; and Holljes and Wagner (*loc. cit.*), m. p. 266—269° for the base. (26) Found for base: C, 74·6; H, 5·4. Calc. for $C_{14}H_{13}ON_2$: C, 75·0; H, 5·4%. Wiedenhagen (*loc. cit.*) gives m. p. 228—230°. (27) Found: C, 58·5; H, 4·4. $C_{13}H_9O_3N_3.1·5H_2O$ requires C, 58·8; H, 4·5%. (28) Kym (*Ber.*, 1900, **33**, 2848) records m. p. 235—236°, and Lauth (*Bull. Soc. chim.*, 1897, **17**, 618), m. p. 240° for the base. Miklaszewski and Niementowski (*Ber.*, 1901, **34**, 2953) record m. p. 240° for the base and m. p. 348° for the dihydrochloride. (29) Found for the base: C, 57·3; H, 4·1; S, 12·4. $C_{13}H_{11}O_2N_3S$ requires C, 57·1; H, 4·1; S, 11·7%. (30) Wiedenhagen (*loc. cit.*) gives m. p. 285—286° for the base. (33) Hübner (*loc. cit.*) does not record a m. p. for this compound. (34) and (36) Oxley and Short (*J.*, 1949, 449). (39) The hydrochloride showed dimorphism, m. p. 143° with rapid heating, recrystallising to m. p. 155°; m. p. 155° with slow heating. (43) Cymerman and Short (*loc. cit.*). (45) The hydrochloride could not be crystallised. (49) Preparation by Dr. Cymerman. (50) Oxley and Short (*J.*, 1949, 449). (51) Cymerman and Short (*loc. cit.*). (52) Preparation by Dr. Cymerman. (53) Cymerman and Short (*loc. cit.*). (60) Preparation by Mr. G. S. Ward. (65) and (66) Preparations by Dr. R. P. Hullin. (68) B. p. 144°/1 mm. (73), (74), and (75) Preparations by Dr. R. P. Hullin.

Method A. A mixture of equimolecular quantities of the appropriate cyanide and substituted ammonium benzenesulphonate was heated with stirring (or under pressure if necessary) at temperatures ranging from 180° to 220° (260—265° when ammonium benzenesulphonate was used) for periods of 2—6 hours (Oxley and Short, *J.*, 1946, 147). The product was either isolated as the benzenesulphonate or converted into the free base by dissolving it in water or ethanol and adding an excess of 5N-sodium hydroxide. The crude amidine could be purified by direct crystallisation or by collection in benzene and extraction from the benzene solution with acetic acid–sodium acetate buffer (pH *ca.* 4·6), which did not extract the arylamine. Basification of the buffer extract then gave the amidine in almost pure condition.

Method B. As for method A, but the substituted ammonium toluene-*p*-sulphonate being used.

Method C. For the preparation of cyclic amidines the cyanide was similarly fused with the appropriate diamine mono-benzenesulphonate or -toluene-*p*-sulphonate [or an equivalent mixture of diamine and diamine di-benzenesulphonate or -toluene-*p*-sulphonate (Oxley and Short, *J.*, 1947, 497)].

Method D. A mixture of cyanide and amine was treated with a molecular equivalent of anhydrous aluminium chloride at 160—200° for 20—60 minutes (Oxley, Partridge, and Short, *loc. cit.*). The free base was liberated by aqueous sodium hydroxide solution and isolated as a suitable derivative.

Method E. A mixture of the appropriate *o*-phenylenediamine and arylaldehyde was oxidised with copper acetate in aqueous ethanol or methanol according to Wiedenhagen's method (*loc. cit.*).

Method F. The corresponding nitro-compound was reduced with ammonium sulphide according to Pinnow and Wiskott (*Ber.*, 1899, **32**, 906).

Method G. A mixture of acetimidoethyl ether (2 mols.) and the amine (1 mol.) was kept at room temperature for 6—24 days, alone or diluted with anhydrous ether. During this time the mixture became strongly alkaline to Titan-yellow. Ether and excess of acetimidoether were removed under reduced pressure, and the amidine isolated either as a suitable derivative or by distillation under reduced pressure.

*Arylammonium Benzenesulphonates and Toluene-*p*-sulphonates.*—The following benzenesulphonates and toluene-*p*-sulphonates used in methods A, B, and C have not previously been described : p-*Butoxyanilinium toluene*-p-*sulphonate*, needles (from *iso*propanol), m. p. 189° (Found : N, 4·3. $C_{17}H_{23}O_4NS$ requires N, 4·15%); 4 : 4′-diaminodiphenyl ether dibenzenesulphonate, m. p. 285° (not analysed); 1 : 2-*di*-(p-*aminophenoxy*)*ethane dibenzenesulphonate*, plates (from water), m. p. 280—281° (Found : N, 5·2. $C_{26}H_{28}O_8N_2S_2$ requires N, 5·0%) [prepared from 1 : 2-di-(*p*-aminophenoxy)ethane, pale buff needles (from aqueous ethanol), m. p. 170—172° (Found : N, 11·5. Calc. for $C_{14}H_{16}O_2N_2$: N, 11·5%). Wagner (*J. pr. Chem.*, 1883, **27**, 206) records m. p. 176°]; 1 : 3-di-(*p*-aminophenoxy)propane dibenzenesulphonate, plates (from ethanol), m. p. 236—238° (not analysed); 1 : 4-*di*-(p-*aminophenoxy*)*butane dibenzenesulphonate*, plates (from ethanol), m. p. 262° (Found : N, 5·0. $C_{28}H_{32}O_8N_2S_2$ requires N, 4·8%); 3-*aminodiphenyl benzenesulphonate*, needles (from water), m. p. 187—188° (Found : N, 4·45. $C_{18}H_{17}O_3NS$ requires N, 4·3%); p-*phenylenediamine dibenzenesulphonate*, needles (from ethanol), m.p. 158° (decomp.) (Found : N, 6·8. $C_{18}H_{20}O_4N_2S_2$ requires N, 6·6%).

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RESEARCH LABORATORIES, BOOTS PURE DRUG CO. LTD.,
NOTTINGHAM.

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105. *Properties of Ion-exchange Resins in Relation to their Structure. Part II. Relative Affinities.*

By D. Reichenberg, K. W. Pepper, and D. J. McCauley.

The relative affinity coefficients (K_H^{Na}) of sodium and hydrogen ions for sulphonated polystyrene resins of different degrees of cross-linking have been determined at 0·1M-cation concentration in solution. For a resin of low cross-linking, K_H^{Na} is approximately unity and independent of the mole-fraction of sodium ion on the resin (X_{Na_R}). With resins of medium cross-linking, K_H^{Na} is greater than unity for all values of X_{Na_R} and shows a flat maximum at a value of X_{Na_R} of 0·4—0·5. For resins of high cross-linking, the maximum disappears and K_H^{Na} decreases sharply with increasing X_{Na_R}, becoming less than unity at high values of X_{Na_R}. Within the series of resins, K_H^{Na} at low values of X_{Na_R} increases with increasing cross-linking.

In general, these results are consistent with Gregor's theory (*J. Amer. Chem. Soc.*, 1948, **70**, 1293) that ion-exchange resins may be regarded as swelling gels, the swelling pressure due to the osmotic activity and hydration of the ionic groupings being balanced by a counter-pressure exerted by the cross-linked polymeric network. The theory fails to account for the decrease of K_{Na}^{H} to values below unity with resins of high cross-linking, and also for the increase in K_H^{Na} with increasing X_{Na_R} with resins of medium cross-linking. Tentative explanations for these effects are suggested.

In Part I of this series (Topp and Pepper, *J.*, 1949, 3299) the titration curves of a series of resins of known preparation were correlated with the properties of the ionizable groups present. The advantages of monofunctional resins (*i.e.*, those containing only one type of ionizable group) in ion-exchange chromatography and in studies of their physicochemical properties were emphasized. Among the most important of these properties is the relative affinity of the resin for different ions. With two exchangeable ions, the difference in affinity is manifested by a difference between the ratio of the amounts of the two ions on the resin and that in a solution in equilibrium with the resin. As a result, the relative affinity is the principal factor determining the ease and efficiency of a separation by ion-exchange chromatography. A knowledge of the relative affinities of different ions for various resins should therefore be of immediate practical value, while at the same time helping towards a better insight into the nature of the ion-exchange process and the structure of the resins.

The importance of relative affinity has long been recognised and has been the subject of much study both with synthetic resins and with other types of exchange materials (natural and artificial zeolites, sulphonated coals, etc.). However, only the most recent work with synthetic resins has a direct bearing on the present research. Boyd, Schubert, and Adamson (*J. Amer. Chem. Soc.*, 1947, **69**, 2818) investigated ion-exchange equilibria with a polyfunctional resin containing phenolic and methylenesulphonic groups, under conditions where the phenolic groups might be expected to play little or no part in the exchange. For the sodium–hydrogen exchange in solution of total cation concentration of 0·1M., they concluded that the relative affinity coefficient, K_H^{Na} (for exact definition of this quantity see below), remained constant within experimental error when the mole-fraction of sodium on the resin (X_{Na_R}) was varied from 0·3 to 0·8. Bauman and Eichhorn (*ibid.*, p. 2830), working with a monofunctional synthetic resin containing nuclear sulphonic groups, investigated the effect of variation of the total cation concentration, using ammonium and hydrogen as cations. They found that $K_H^{NH_4}$ remained constant at a value of 1·2 for solutions below 1M., but decreased with increasing cation concentration, becoming 0·5 at 4M.* Duncan and Lister (*J.*, 1949, 3285) investigated the sodium–hydrogen exchange on a similar resin in solutions of total cation concentration 0·2M. They found that K_H^{Na} did not remain constant with varying X_{Na_R}, there being a maximum at a value of X_{Na_R} of about 0·1. They also found (*Faraday Soc. Discussions*, 1949, No. 7, 104) a similar variation of K when other pairs of cations were used (barium–hydrogen and lanthanum–

* In these experiments $K_H^{NH_4}$ was not corrected for activity coefficients in solution.

hydrogen). Cosgrove and Strickland (*J.*, 1950, 1845) investigated the exchange of potassium–hydrogen, ammonium–hydrogen, and potassium–ammonium on two resins, one of which was a sulphonated cross-linked polystyrene prepared in this laboratory. In all cases when the mole-fraction of cation on the resin was increased from 0·2 to 0·8, the relative affinity for that cation fell markedly.

The general aim of the present work was to investigate the effect on affinity of variation in the polymer structure of the resin, in particular the degree of cross-linking. Sulphonated cross-linked polystyrene resins are particularly suitable for such a study, since the degree of cross-linking may be readily controlled and varied by varying the proportion of cross-linking agent—divinylbenzene in the present instance. It is known that the degree of cross-linking markedly affects other properties of these resins, *e.g.*, the swelling in water and the rates of exchange (Pepper, *J. Soc. Chem. Ind.*, in the press). Kunin and Myers (*Faraday Soc. Discussions*, 1949, No. 7, 114) have shown that with anion-exchange resins both the swelling and the effective capacity for large anions decrease markedly with increase of cross-linking, and there was also an increase of affinity for fluoride, chloride, and iodide ions relative to hydroxyl ions. Samuelson (*Ingen. Vetensk. Akad.*, 1944, No. 179), working with a very highly swollen sulphonated polystyrene resin, found that the values of K for the exchange reactions hydrogen–sodium, hydrogen–potassium, and hydrogen–tetramethylammonium were all unity within experimental error.*

Various theoretical treatments have been given of the equilibria of ion-exchange. However, all that can, in fact, be measured in a given system containing two exchangeable ions, A and B (which, for simplicity, we will suppose to be of the same valency), is the quantity K_A^B, defined as follows:

$$K_A^B = \frac{[B_R]}{[A_R]} \cdot \frac{[A_S]}{[B_S]} \cdot \frac{f_{A_S}}{f_{B_S}}$$

where $[A]_R$ and $[B]_R$ are the amounts of A and B on the resin, $[A_S]$ and $[B_S]$ are the concentrations in solution, and f_{A_S} and f_{B_S} are the activity coefficients in solution. K_A^B has been called the "thermodynamic equilibrium constant" of the exchange reaction $A_R + B_S \rightleftharpoons B_R + A_S$. This is permissible provided it is understood that K_A^B may, in principle, vary with X_{B_R}, *i.e.*, $[B_R]/([A_R] + [B_R])$. We prefer, however, the name "relative affinity coefficient" and this term will be used throughout the present work.

The present paper deals with the relative affinity coefficients of sodium and hydrogen ions for sulphonated polystyrene resins cross-linked with varying amounts of divinylbenzene. Experimentally, the problem resolved itself into measuring $[Na_R]/[H_R]$ and $[Na_S]/[H_S]$. The method used in the present work consisted essentially of preparing a series of "conditioning solutions" each having a known value of $[Na_S]/[H_S]$ (but all of the same total cation concentration) and treating a fixed quantity of the resin, of known exchange capacity, with one of the solutions until the resin was in equilibrium with the solution. $[H_R]$ was then determined directly by displacement with excess of neutral sodium chloride, $[Na_R]$ being obtained from the difference between the known exchange capacity of the resin and $[H_R]$. The experiments were all carried out at room temperature (22—25°) and in solutions of total cation concentration 0·1125M.

Experimental.

Materials.—Resins. The preparation of the resins examined, sulphonated cross-linked polystyrenes in bead form, has been described in detail (Pepper, *loc. cit.*). Briefly, a mixture of styrene and divinylbenzene solution with 1% of benzoyl peroxide as catalyst was heated in aqueous suspension at 80° for 18 hours. The resulting copolymer was sulphonated by treatment with concentrated sulphuric acid at 100° in presence of 1% of silver sulphate. The products were washed, treated alternately with 2M-sodium chloride and 2N-hydrochloric acid two or three times, and finally sieved. The divinylbenzene solution was a commercial supply and consisted of divinylbenzene (*ca.* 33%) in ethylstyrene (*ca.* 66%) with a little saturated material. The divinylbenzene contents of resins given in this paper are nominal; the proportions of divinylbenzene solution and styrene were varied systematically but the composition of the divinylbenzene solution was not known accurately and it has not been proved that the three monomers styrene, ethylstyrene, and divinylbenzene copolymerise uniformly in all proportions. Unambiguous evidence of the increase in degree of cross-linking resulting from increase in nominal divinylbenzene content is, however, provided by the marked reduction in swelling shown in Table I. The observed specific exchange capacities of the resins (except that containing 33% of divinylbenzene)

* After this work had been commenced, we learnt that Dr. W. C. Bauman was engaged on a similar investigation and also had observed the marked influence of the degree of cross-linking on relative affinities.

agree closely with those calculated on the assumption that the monomers copolymerise uniformly and that each benzene ring in the copolymer contains one sulphonic acid group.

TABLE I.

Properties of resins.

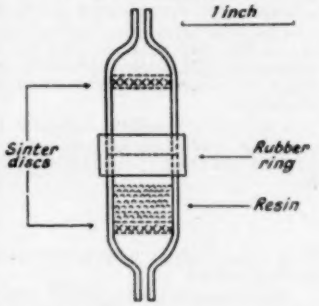
Nominal divinylbenzene content, %.	Particle-diameter, μ. (wet).	Swelling (g. of H_2O per g. of dry H^+ resin).	Specific exchange capacity * (mg.-equivs. per g. of dry H^+ resin): Obs. (±0·05).	Calc. for mono-sulphonic acids.
2	250—200	3·35	5·40	5·39
5	400—300	1·45	5·30	5·34
10	500—400	0·80	5·15	5·24
17	400—250	0·57	5·00	5·11
33	200—100	0·55	4·25	4·74

* These specific exchange capacities were obtained on samples of the resins used for the affinity determination by estimation of hydrogen ion displaced from a known dry weight in equilibrium with a solution of $[Na_s]/[H_s]$ ratio about 1000. The values quoted previously (Pepper, *loc. cit.*) were the means obtained in alkaline solution for several preparations at each nominal divinylbenzene content. The determinations in alkaline and slightly acid solution agreed within experimental error except in the case of the 17% and 33% resins. In alkaline solution, the latter resins gave values of 5·15 and 4·60 mg.-equivs. per g.

Conditioning solutions. Approx. 2N-hydrochloric acid and 2N-sodium hydroxide solutions were made with AnalaR chemicals, and their relative concentrations obtained by titration. The acid was standardised independently and found to be 2·25N. For each conditioning solution, appropriate volumes of the acid and the alkali solutions were made up to 2 l. with water. These solutions (of total cation concentration 1·125M.) were kept as stock solutions and when required for an affinity determination were diluted ten-fold (*i.e.*, to 0·1125M.). The relative strengths of the acid and the alkali solutions and the volumes of each used in making up a given conditioning solution being known, the ratio $[Na_s]/[H_s]$ could be readily calculated. However, for conditioning solutions of high $[Na_s]/[H_s]$ a small error in the value for the relative strengths of acid and alkali, or in either of their volumes, would cause an appreciable *relative* error in $[Na_s]/[H_s]$. In these cases, the stock conditioning solutions (1·125M.) were themselves titrated against some approx. 0·05N-sodium hydroxide which was in turn standardised against the original 2·25N-acid. These titrations gave directly the ratio $([Na_s] + [H_s])/[H_s]$ for the conditioning solution, from which an accurate value of $[Na_s]/[H_s]$ was calculated. This procedure was carried out with conditioning solutions of decreasing $[Na_s]/[H_s]$ until the value so obtained agreed exactly with that calculated by the former method. The conditioning solutions used for affinity determinations covered a range of $[Na_s]/[H_s]$ from 0·02 to 50.

FIG. 1.

Diagram of apparatus.



When this work was commenced, ordinary distilled water was used for the preparation of solutions and for washing the resin. Later, conductivity-grade water obtained by mixed-bed deionization became available in quantity and was used in preference.

Determination of Relative Affinity Coefficients.—Apparatus. The resin was contained in a small column made from two glass tubes fitted with sealed-in sintered discs (porosity 1). The glass tubes were cut to within 1 in. of the sinters, and the ends ground flat. The tubes were then fitted together with a rubber ring which sealed the joint (Fig. 1). This apparatus permitted agitation and backwashing of the resin without loss of material.

Method. An amount of resin having a capacity of about 2·5 mg.-equivs. (0·5 g. of air-dry material) was introduced into the apparatus, and 250—500 ml. of 0·1M-conditioning solution (*i.e.*, about 10—20 times the capacity of the sample) were passed through the resin at a flow-rate of *ca.* 100 ml./hour. For the more highly cross-linked resins (17% and 33% nominal divinylbenzene content), which exchange more slowly, 1 l. of conditioning solution was passed during 12 hours. To avoid channelling and to ensure complete mixing, the resin was back-washed at about half-hourly intervals. Trouble was sometimes experienced owing to the liberation of dissolved air bubbles which subsequently tended to adhere to the resin and prevent free access of fresh solution. This difficulty was obviated by back-washing the resin (before conditioning) with a 0·1% solution of Lissapol N (a non-ionic detergent), followed by washing with water. After the conditioning, the apparatus was drained by a standard procedure, air being sucked through for 1 minute at 10 ml./second. The resin was then washed to neutrality, the washings being collected and titrated with the standard 0·05N-sodium hydroxide. Finally, the *combined* hydrogen was displaced from the resin with neutral 0·5M-sodium chloride, and the effluent collected and titrated. For all these titrations, the indicator used was a mixture of methyl-red and bromocresol-green in alcohol (Kolthoff and Stenger, "Volumetric Analysis," Vol. II, 1947, p. 58). This had a titration exponent of 5·1 and under the conditions used was virtually unaffected by carbon dioxide.

Careful consideration was given to the removal of conditioning solution left in the apparatus after drainage. The greater part of this residual electrolyte was held in the two sintered discs, but some would

be retained between beads of resin and possibly, to a small extent, within the resin itself (Bauman and Eichhorn, *loc. cit.*). The following subsidiary experiments proved that during washing the relative amounts of *combined* sodium and hydrogen remained unchanged. In determining the capacity of a sample, the resin was first converted into the hydrogen form by using 0·1125N-hydrochloric acid. After the standard drainage procedure, the sample was washed and the washings titrated as in an affinity determination. For each sample of resin, this titre (t_w) was closely reproducible. Since washing would not be expected to remove *combined* hydrogen from the hydrogen form of the resin, the titre t_w must represent the amount of hydrogen in the residual electrolyte referred to above. The total amount of residual electrolyte is likely to be dependent only on the total cation concentration and independent of X_{H_S} and should therefore be the same in an affinity as in a capacity determination. Hence, provided that the amount of combined hydrogen on the resin did not alter during washing, the titre of the washings in an affinity determination (X_{H_S} of conditioning solution <1) should be equal to $t_w X_{H_S}$. This was confirmed experimentally in all cases, proving that the only hydrogen removed during washing was that due to residual electrolyte.

The overall accuracy of the determinations of K_H^{Na} is considered to be $\pm 2\%$ for values of X_{Na_R} from 0·2 to 0·9; outside this range, it is $\pm 10\%$ for the 17% and 33% divinylbenzene resins and $\pm 5\%$ for those of lower divinylbenzene content. At low X_{Na_R}, $[Na_R]$ is given by the small difference between two large titres. A small error in either would produce a large relative error which increases as the difference between the titres decreases. To reduce the effect of any systematic error, which would give an erroneous plot for K_H^{Na} against X_{Na_R} at low values of X_{Na_R}, the capacity and affinity determinations were carried out by the same method. At high values of X_{Na_R}, the accuracy was limited by the small volume of the hydrogen titre. Any resulting error was reduced by using standardised 0·01N-sodium hydroxide for these titrations.

A slight decrease in the capacity of the resin was observed during a series of experiments; *e.g.*, for a 10% divinylbenzene resin, the loss was 0·7% after 60 cycles. To avoid possible errors due to this effect, capacity determinations were interspersed between affinity determinations; thus the capacity appropriate to each affinity determination was known.

Complete attainment of equilibrium between resin and conditioning solution was checked in at least one of two ways: (*a*) doubling the volume of conditioning solution passed at the same flow-rate, (*b*) starting the conditioning with the resin in the hydrogen instead of the sodium form. In all cases the results were found to be independent of these variations in procedure and no evidence was found of any hysteresis.

Correction for activity coefficients in solution. The values of the ratio f_{H_S}/f_{Na_S} for the various conditioning solutions were calculated by using published data on activity coefficients in mixed solutions (Harned and Owen, "Physical Chemistry of Electrolytic Solutions," New York, 1943, p. 450 *et seq.*). Now

$$\frac{f_{H_S}}{f_{Na_S}} = \frac{f_{H^+} f_{Cl^-}}{f_{Na^+} f_{Cl^-}} = \frac{(\gamma_{HCl\pm})^2}{(\gamma_{NaCl\pm})^2}$$

the γ terms referring to *mean ion activity coefficients* (which are the quantities usually given in tables of published data).

With NaCl–HCl mixtures of total concentration 0·1125M. (0·1130 molal), we calculate that for $X_{Na_S} = 0$, $f_{H_S}/f_{Na_S} = 1{\cdot}022$, and for $X_{Na_S} = 1$, $f_{H_S}/f_{Na_S} = 1{\cdot}029$. For our present purpose, it is sufficiently accurate to take f_{H_S}/f_{Na_S} as being a linear function of X_{Na_S} between these limits.

Results and Discussion.

In Figs. 2—6, values of K_H^{Na} have been plotted as functions of X_{Na_R} for resins containing nominally 2%, 5%, 10%, 17%, and 33% of divinylbenzene. The following conclusions may be drawn. (*a*) With the resin of *low* cross-linking (2% divinylbenzene, Fig. 2) K_H^{Na} is approximately unity for all values of X_{Na_R}. (*b*) With the resins of *medium* cross-linking (5% and 10% of divinylbenzene, Figs. 3 and 4), K_H^{Na} increases with X_{Na_R} at low values of X_{Na_R} and shows a flat maximum at about $X_{NaR} = 0{\cdot}4$—$0{\cdot}5$. In the range $X_{Na_R} = 0$—$0{\cdot}5$, K_H^{Na} increases with the degree of cross-linking. With both resins, K_H^{Na} is greater than unity at all values of X_{Na_R}. (*c*) With the resins of *high* cross-linking (17% and 33% of divinylbenzene, Figs. 5 and 6) the maximum disappears. K_H^{Na} has a high value at low values of X_{Na_R} and decreases with increasing X_{Na_R}, becoming less than unity at high values of X_{Na_R}. The higher the cross-linking, the greater is the value of K_H^{Na} at low X_{Na_R} and the smaller its value at high X_{Na_R}.

In our view, two important theoretical interpretations of ion-exchange equilibria may be distinguished, *viz.*, Jenny's treatment (*J. Physical Chem.*, 1932, **36**, 2217) as developed by Boyd, Schubert, and Adamson (*loc. cit.*) and by Kressman and Kitchener (*J.*, 1949, 1190), and Gregor's theory (*J. Amer. Chem. Soc.*, 1948, **70**, 1293). According to the former view, the equilibria are governed by the electrical energy gained or lost on replacing one cation by another. For ions of the same valency, this energy change will be determined mainly by the

FIG. 2.
2% *Nominal divinylbenzene content.*

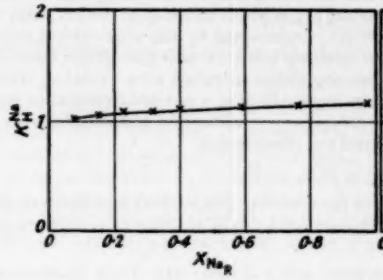


FIG. 3.
5% *Nominal divinylbenzene content.*

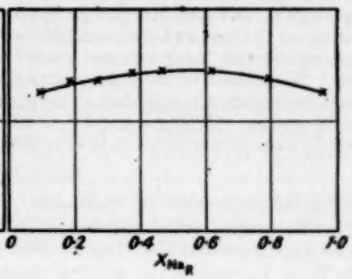


FIG. 4.
10% *Nominal divinylbenzene content.*

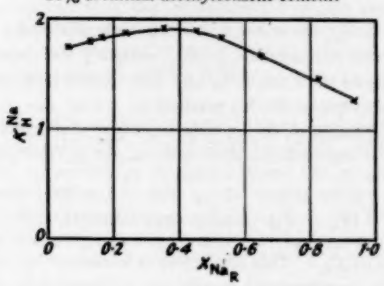


FIG. 5.
17% *Nominal divinylbenzene content.*

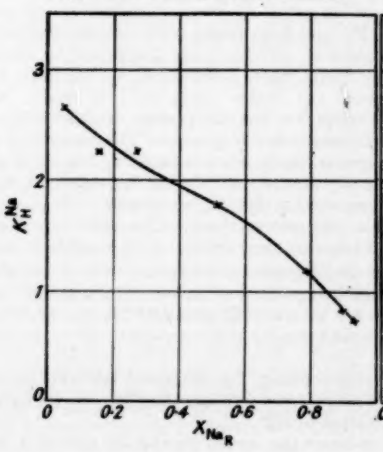
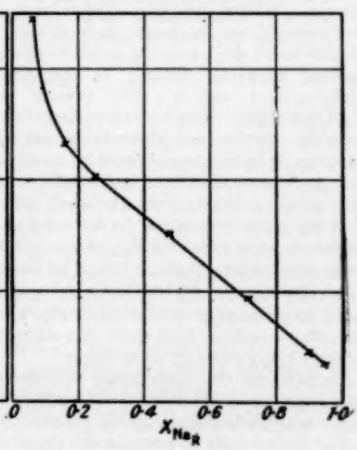


FIG. 6.
33% *Nominal divinylbenzene content.*



" distance of closest approach " of the cation to the bound anionic group, which in turn will depend on the effective radius of the cation. It is important to note that this effective radius is that of the ion in the state of hydration in which it exists in the resin.

Gregor regards an ion-exchange resin as a swelling gel in which swelling of the dry resin (owing to hydration of the ions and their osmotic activity) is restrained by the cross-linked polymeric structure, equilibrium being attained when the swelling pressure and the elastic restraint are balanced. The essence of the theory is to treat the resins in terms of a model in which the elastic counter-pressure is regarded as having the same effect as a normal external pressure on an osmotic system. Making a number of simplifying approximations and assumptions in the equations for osmotic equilibrium, Gregor deduced the relationship

$$\boldsymbol{RT} \ln K_{\mathrm{A}}^{\mathrm{B}} = p(\bar{V}_{\mathrm{A}} - \bar{V}_{\mathrm{B}})$$

where $K_{\mathrm{A}}^{\mathrm{B}}$ is the relative affinity coefficient, p is the swelling pressure at equilibrium, and $\bar{V}_{\mathrm{A}}$ and $\bar{V}_{\mathrm{B}}$ are the partial molal volumes of the hydrated cations in the resin. The following deductions may be derived from Gregor's theory.

(1) If $\bar{V}_{\mathrm{A}} > \bar{V}_{\mathrm{B}}$, then $K_{\mathrm{A}}^{\mathrm{B}} > 1$. This deduction, which follows also from Jenny's theory, is in general agreement with experimental results on strongly acidic resins. In the present work, the values of $K_{\mathrm{H}}^{\mathrm{Na}}$ were greater than unity (except with resins of high cross-linking at high $X_{\mathrm{Na_R}}$) in accord with the view that the hydrogen ion in solution is larger than the sodium ion owing to its higher degree of hydration. This is probably true in the resin under normal conditions.

(2) If $\bar{V}_{\mathrm{A}} > \bar{V}_{\mathrm{B}}$, then, as $X_{\mathrm{B_R}}$ increases, the resin contracts and p decreases. If $\bar{V}_{\mathrm{A}}$ and $\bar{V}_{\mathrm{B}}$ remain roughly constant and independent of $X_{\mathrm{B_R}}$, then $K_{\mathrm{A}}^{\mathrm{B}}$ will decrease. The decline in $K_{\mathrm{H}}^{\mathrm{Na}}$ with increasing $X_{\mathrm{Na_R}}$ observed with the 17% and 33% resins (and also with the 5% and 10% resins at high $X_{\mathrm{Na_R}}$) is consistent with this prediction.

(3) For a given ionic composition, the equilibrium value of p depends on the elastic properties of the resin. The greater the degree of cross-linking, the greater will be the elastic modulus and the smaller the volume of the swollen resin at equilibrium. Hence the concentration of osmotically active groups will be greater and p will be greater. Hence, the higher will be the numerical value of $\ln K_{\mathrm{B}}^{\mathrm{A}}$, if $(\bar{V}_{\mathrm{A}} - \bar{V}_{\mathrm{B}})$ remains approximately constant for resins of different cross-linking. Conversely, a resin of very low cross-linking should have a value of $K_{\mathrm{A}}^{\mathrm{B}}$ nearly equal to unity for all values of $X_{\mathrm{B_R}}$. This prediction is borne out by the results for the 2% resin.

We now consider those experimental results not satisfactorily covered by this simplified version of Gregor's theory.

(*a*) Although the theory predicts a decline in $K_{\mathrm{H}}^{\mathrm{Na}}$ with increasing $X_{\mathrm{Na_R}}$, it does not predict the drop in $K_{\mathrm{H}}^{\mathrm{Na}}$ below unity at high values of $X_{\mathrm{Na_R}}$ (Figs. 5 and 6). It is considered that this effect may be due to the presence in these two resins of acidic groups other than the sulphonic acid groups. Whilst complete sulphonation of the resins of lower cross-linking was achieved in a few hours, it was necessary to heat the 17% and 33% resins with concentrated sulphuric acid at 100° for 7 days and the possible formation of carboxylic groups cannot be overlooked. The specific exchange-capacity of the 33% resin when determined in alkaline solution ($[\mathrm{Na_S}]/[\mathrm{H_S}] \sim 10^{11}$) was 6—10% greater than the value obtained in acidic solution ($[\mathrm{Na_S}]/[\mathrm{H_S}] \sim 1000$). The corresponding difference for the 17% resin was 2—3%. These data indicate the presence of small amounts of weakly acidic groups. The amount of sodium ion taken up by such groups would be small from conditioning solutions of $[\mathrm{Na_S}]/[\mathrm{H_S}]$ of 50 or less but, in the analysis of the resins with neutral 0·5M-sodium chloride, hydrogen ion might be displaced to some extent from the weak groups, thus giving higher values of $[\mathrm{H_R}]$ and lower values of $K_{\mathrm{H}}^{\mathrm{Na}}$ than correspond to the sulphonic acid groups alone. The effect would be more pronounced at high values of $X_{\mathrm{Na_R}}$ where $[\mathrm{H_R}]$ becomes very small. It is possible to calculate what amount of hydrogen ion displaced from weak groups is necessary to give the observed values of $K_{\mathrm{H}}^{\mathrm{Na}}$, the true $K_{\mathrm{H}}^{\mathrm{Na}}$ for sulphonic groups being taken as unity. The required amounts (expressed as percentages of the capacities) are 6% for the 33% resin and 2% for the 17% resin. We conclude, therefore, that there may be sufficient weakly acidic groups in these two resins to account for the drop in $K_{\mathrm{H}}^{\mathrm{Na}}$ below unity.

In contrast, for the three resins of lower cross-linking, the difference between the specific exchange capacity in alkaline solution and in acid solution was less than 2%, an amount which can have negligible influence on the observed values of $K_{\mathrm{H}}^{\mathrm{Na}}$.

(*b*) The theory fails to account for those parts of the curves for the 5% and 10% divinyl-

benzene resins where K_H^{Na} *increases* with increasing X_{Na_R} (Figs. 3 and 4). Gregor considers only the effect of the pressure due to the elastic network on the relative affinities of ions. However, there will be also an internal effect due to ionic interactions. In general, we may write :

$$K_A^B = (K_A^B)_{int.} \cdot (K_A^B)_{ext.}$$

Following Bauman and Eichhorn (*loc. cit.*) we may put

$$(K_A^B)_{int.} = (f_{A_R}/f_{B_R})_{int.}$$

The latter quantity is analogous to the ratio of the activity coefficients of two ions in mixed solutions at normal pressure. The ratio $(f_{H_R}/f_{Na_R})_{int.}$ might be expected therefore to show similar *qualitative* features to the ratio f_H/f_{Na} for solutions of mixed salts at total cationic concentration comparable to that in the resin (1·5—8 molal, calculated on the basis of g.-equivs. per 1000 g. of absorbed water, cf. Table I). Values of f_H/f_{Na} calculated from published data on solutions of NaCl–HCl mixtures at various concentrations are as given below (Harned and Owen, *loc. cit.*; Robinson and Stokes, *Trans. Faraday Soc.*, 1949, **45**, 612).

Molality.		0·1.	0·2.	1·0.	3·0.	5·0.
f_H/f_{Na}	$X_{Na} = 0$	1·020	1·033	1·161	1·524	1·951
	$X_{Na} = 1$	1·026	1·050	1·308	2·213	3·715

At all concentrations f_H/f_{Na} increases with increasing X_{Na}. It may well be that this result holds qualitatively for the ions in the resin, thus accounting for the increase observed in K_H^{Na}.

In conclusion, it would appear that the experimental results are generally consistent, at least qualitatively, with Gregor's theory, but that a complete interpretation requires consideration of both internal and external effects.* In an attempt to elucidate these effects, a study of equilibria with other pairs of cations is being made.

The work described above was carried out as part of the research programme of the Chemical Research Laboratory, and this paper is published by permission of the Acting Director of the Laboratory. The authors thank Dr. J. F. Duncan of the Atomic Energy Research Establishment and Dr. J. A. Kitchener of Imperial College, London, for helpful discussions.

CHEMICAL RESEARCH LABORATORY,
TEDDINGTON, MIDDLESEX.

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106. *The Selective Absorption of Optical Antipodes by Proteins.*

By WILLIAM BRADLEY and GERALD C. EASTY.

Both wool and casein selectively absorb (+)-mandelic acid from an aqueous solution of (±)-mandelic acid at room temperature. (+)-α-Naphthylglycollic acid is selectively absorbed by wool from an aqueous alcoholic solution of the (±)-acid.

The significance of these results is discussed.

THE possibility that optical antipodes might be absorbed by proteins to different degrees appears to have been considered first by Willstätter (*Ber.*, 1904, **37**, 3758). He brought together wool and an aqueous solution of racemic tropacocaine, atropine, or homatropine but in no instance was the selective absorption of an optically active form observed. Ingersoll and Adams (*J. Amer. Chem. Soc.*, 1922, **44**, 2930) extended the study to weak acids. They prepared two azo-dyes by diazotising the (+)- and the (−)-form of α-*p*-aminobenzamido-α-phenylacetic acid and coupling the products with dimethylaniline. In preliminary experiments it was considered that the two dyes were absorbed by wool at different rates, but a more extensive investigation by Brode and Adams (*ibid.*, 1926, **48**, 2193, 2202) led to the conclusion that the rate of absorption of the two antipodes was the same. Earlier, Porter and Hirst (*ibid.*, 1919,

* Dr. E. Glueckauf (*Nature*, 1950, **166**, 775, and private communication) has recently developed a theory which accounts for the decrease in K_H^{Na} with increasing X_{Na_R} and for the increase in selectivity with increase in the degree of cross-linking. According to this view, the predominant factor is not elastic forces of the network acting on the internal system but rather a combination of ion hydration and ion-pair formation between cations and resin anions. The degree of ion-pair formation is modified by the nature of the neighbouring cations, and is thus dependent on composition.

41, 1264) had referred to the partial resolution of a racemic dye by selective absorption on wool, and Porter and Ihrig (*ibid.*, 1923, **45**, 1990) showed that the optically active forms of the azo-compound obtained by diazotising (+)- and (−)-*m*-aminomandelic acid and coupling the products with β-naphthol combined with wool at different rates. Brode and Adams (*loc. cit.*) and Henderson and Rule (*J.*, 1939, 1568) were unable to confirm Porter and Ihrig's work. Morgan and Skinner (*J.*, 1925, 1731) showed that the (−)-form of 2 : 3-di-[*p*-(*p'*-sulphophenylazo)anilino]butane was less rapidly absorbed by wool than the (+)-form. Brode and Adams (*loc. cit.*) have pointed out, however, that the difference in the observed rates was within experimental error. Brode and Adams reached the conclusion that in no known case was one dye absorbed more rapidly than its mirror image or an active solution produced by contact of a racemic dye solution with wool or silk. In the meantime von Euler and Bucht (*Z. anorg. Chem.*, 1923, **126**, 269) showed that α-bromopropionic acid was absorbed by casein but that under the conditions employed selective absorption could not be observed. In a later investigation Brode and Adams (*J. Amer. Chem. Soc.*, 1941, **63**, 923) applied to wool and a synthetic fibre the (+)-, (−)-, and (±)-forms of the bisazo-compound derived by combining 2 : 2'-diamino-1 : 1'-dinaphthyl with phenyl-J-acid; there was no evidence of selective absorption. Recently, Kögl, Faber, and de Boer (*Rec. Trav. chim.*, 1950, **69**, 482) have prepared two stereoisomeric colouring matters by condensing tetra-aminophenazine with the (+)- and the (−)-form of camphorquinone; the two isomers showed no significant difference in absorption by animal tissues, either normal or malignant.

Brode and Adams (*loc. cit.*, 1941) remarked that the structure of the colouring matters used in tests for selective absorption might not have been the most suitable for the purpose. Kögl, Faber, and de Boer (*loc. cit.*) expressed a similar view in regard to their own experiments. It was considered that the asymmetric centres of the dyes were too far removed from their point of attachment to the tissues for asymmetry to have influenced the absorption process or the properties of the resulting complex. The difficulty of observing selective absorption is greater when the specific rotation of the test substance is low (von Euler and Bucht, *loc. cit.*). Particular interest attaches therefore to the work of Martin and Kuhn (*Z. Electrochem.*, 1941, **47**, 216) who investigated the absorption of mandelic acid on wool. Their experiments included a temperature effect, the wool being used in the form of a continuous strip which traversed in turn a cold and a hot aqueous solution of mandelic acid. The development of a lævorotatory solution was observed in several experiments but the results were variable. Regarding the degree of resolution achieved, the authors observe " Er ist so klein dass es schwierig sein würde ihn unmittelbar zu beobachten."

In the present investigation a study has been made of the absorption of mandelic acid on wool from an aqueous solution at room temperature. In preliminary experiments wool was first extracted by means of organic solvents and then brought into contact with dilute aqueous solutions of acetic and chloroacetic acids. In each instance a lævorotatory solution was obtained. This result indicates how doubtful may be the value of observations which consist solely in determining the rotation of solutions left in contact with wool. In the main experiments wool purified by solvent extraction was immersed in a cold aqueous solution of (±)-mandelic acid. The solution became lævorotatory and from it was isolated mandelic acid having in a typical experiment α_D −0·45°. The process of isolation consisted in recovering the solute, extracting it with ether, dissolving the ether-soluble portion in benzene, and adsorbing it from the benzene solution on a column of alumina. Washing with benzene containing 1—5% of acetone removed impurities, and then the mandelic acid was recovered from the column by extraction with dilute hydrochloric acid. Finally, it was extracted from the acid solution into ether. Separate experiments proved that none of the stages of purification brought about the resolution of (±)-mandelic acid; in fact a slight loss of activity was generally observed. Mandelic acid absorbed by the wool was then recovered by extraction with dilute aqueous ammonia or dilute hydrochloric acid and then taken into ether. The ether-soluble portion was transferred to benzene, then purified by adsorption on alumina, washing with benzene containing 1—5% of acetone, the mandelic acid being recovered as before by extraction with dilute hydrochloric acid and transference into ether. In a typical experiment mandelic acid recovered from wool had $[\alpha]_D$ +0·6°. The effect of ammonia in the process of isolating mandelic acid was studied in separate experiments. It was shown that dilute ammonia in contact with wool gave solutions that were always lævorotatory. The isolation of both lævorotatory and dextrorotatory mandelic acid in these experiments establishes the selective absorption of dextrorotatory mandelic acid from its aqueous solution by wool.

The experiments with wool have been extended to casein. A sample of casein purified by

means of organic solvents readily gave lævorotatory solutions when extracted in the cold with dilute acetic, chloroacetic, or benzoic acid or ammonia. In contact with solvent-extracted casein an aqueous solution of (±)-mandelic acid became lævorotatory and the process of purification adopted in the experiments using wool gave lævorotatory mandelic acid. In this instance the mere observation of lævorotation in the solution is valueless because of the high specific rotation of casein. A few milligrams of casein in solution cause lævorotation of the same magnitude as that due to the residual mandelic acid. Mandelic acid absorbed by the casein was extracted by means of dilute ammonia, and recovered and purified as described in the experiments using wool. It proved to be dextrorotatory with $[\alpha]_D$ +0·8°.

Experiments with a second sample of good quality commercial casein gave much smaller resolutions. After the casein had been powdered, however, resolutions were obtained which approached those afforded by the first sample. A third sample gave resolutions of the same order as the first. The amount of mandelic acid absorbed and the degree of resolution attained depended on the particle size. One sample of casein was divided into 30/40- and 150/200-mesh portions, each of which was treated as just described. The mandelic acid recovered from the aqueous solution in contact with the coarser casein had α_D −0·02°, that from the more finely divided casein mixture had α_D −0·10°. A second sample of casein, divided into 50/60- and <200-mesh portions, similarly gave unabsorbed acid having −0·02° and −0·06°, respectively. In each experiment the absorbed mandelic acid was also recovered; its dextrorotation was higher the more finely divided the casein had been.

The resolution of mandelic acid on wool and casein supports the view that the first result of the interaction of acids and proteins is the formation of a protein–acid salt, the process being analogous in principle to the resolution of acids by means of active alkaloids. No resolution could be detected when a synthetic polyamide (nylon) was used instead of wool or casein. Resolution on wool or casein does not rigidly prove the occurrence of salt formation with acids, as was once believed (*locc. cit.*; Willstätter; Ingersoll and Adams; Brode and Adams, 1924; Porter and Ihrig), for resolutions have been achieved on optically active neutral substrates. Tsuchida, Kobayashi, and Nakamura (*Bull. Chem. Soc. Japan*, 1936, **11**, 38) have shown that (±)-chlorobis(dimethylglyoxime)amminocobalt can be resolved on quartz, and Kayagunis and Coumolos (*Nature*, 1938, **142**, 162) have demonstrated the resolution of the chromium complex $Cr[(en)_3]Cl_3$ on the same substrate. Moreover, Henderson and Rule have resolved (±)-*p*-phenylenebisiminocamphor on activated lactose. In the present experiments it was found that mandelic acid in benzene–light petroleum could not be resolved on lactose or quartz, but the result may have been determined by very small adsorption.

In further experiments it has been shown that α-naphthylglycollic acid also is partly resolved when its solution in aqueous alcohol is brought into contact with wool. In one experiment the adsorbed acid had $[\alpha]_D$ +1·0°.

It is probable that the selective absorption of optical antipodes of resolvable acids shown by wool and casein will be shown also by many other proteins yet to be studied. In this connection the increase in resolving power of a given weight of a protein with decrease in particle size is of interest. It would suggest that the thin membranes of proteins which occur in natural structures may have in relation to their mass a very marked capacity for the selective absorption of optically active anions.

Experimental.

The optical rotations of the solutions referred to in the following experiments were measured at room temperature in a 2-dm. fixed-end-plate polarimeter tube containing 17·5 c.c. of solution, and values of α_D quoted are thus for $l = 2$. The end-plate error of the polarimeter tube was less than 0·005°. The source of illumination was a sodium-vapour lamp. Each optical reading was the mean of ten observations, the total maximum deviation never exceeding 0·01°. The polarimeter was a "Hilger" model, Type M 413. It afforded ample intensity of illumination with maximum sensitivity with the colourless or pale yellow solutions examined.

The mandelic acid was supplied by British Drug Houses, Ltd. Before use it was recrystallised twice from benzene. The m. p. was 118·5°.

The casein employed in most of the experiments was described as "calcium free" (B.D.H.). Before use it was extracted (Soxhlet) with absolute alcohol for 8 hours, and then with ether for the same period. Finally, the solvent was removed by heating the casein at 100° for 2 days. The purified casein was then kept in a vacuum-desiccator at 1—2 mm. pressure until required.

The wool was used in the form of long unwoven fibres or woven material. In either case the wool, generally about 50 g., was extracted with ether in a Soxhlet for 8 hours and then with absolute alcohol for the same period, to remove oils and grease. It was washed with five or six 3-l. portions of distilled water and then kept in 3 l. of very dilute acetic acid for 1 hour to remove traces of soluble material which was generally present in our samples of wool. The wool was finally washed with ten 3-l. portions of

distilled water and dried in a current of warm air for 6 hours. It was stored over calcium chloride in a desiccator until required.

Absorption of Mandelic Acid on Wool.—In a typical experiment 60 g. of purified wool fibres were immersed in 1 l. of a solution of 30 g. of (±)-mandelic acid in distilled water. The containing flask was stoppered and then kept at the room temperature for 10 days. The solution was separated by filtration, the wool washed with two 200-c.c. portions of distilled water and squeezed as dry as possible The filtrate and washings were combined and then concentrated to 35 c.c. The resulting solution was pale yellow, and had α_D −0·33°.

The total solution was evaporated to dryness, the residue dried in a desiccator over calcium chloride for 1 day, and then digested with dry ether and passed through a fine-mesh sintered-glass filter. A whitish residue gave a strongly positive result in the ninhydrin test. The filtrate was evaporated to dryness and the residue dissolved in absolute ethyl alcohol, to give 35 c.c. of pale yellow solution, having α_D −0·30°.

The ether-insoluble residue, dissolved in warm 3·5% hydrochloric acid (18 c.c.) and cooled, had α_D −0·07°.

The optically active alcoholic solution was evaporated to dryness and the residue recrystallised from toluene. The resulting crystals (m. p. 118·5°) were dissolved in ethyl alcohol to give 17·5 c.c. of a colourless solution, having α_D −0·02°.

The toluene mother-liquor was evaporated to dryness, and the residue dissolved in ethyl alcohol to give 17·5 c.c. of a solution having α_D −0·55°. The solution was then evaporated to dryness, the residue dissolved in cold benzene, and the solution passed through a column of alumina. Two pale brown bands formed, the one narrow and sharp, the other broad and diffuse. The bands were eluted with benzene containing 5% of acetone and then with acetone, and the combined eluates concentrated to 18 c.c.; the solution had α_D −0·02°.

The alumina column was extruded, digested with cold 3·5% hydrochloric acid, and the digest filtered. The fitrate was extracted three times with twice its volume of ether and the ethereal extracts were combined and evaporated to dryness. The residue, recrystallised from a small quantity of benzene, had m. p. 118°. The mandelic acid was dissolved in ethyl alcohol to give 17·5 c.c. of a solution, having α_D = −0·45°.

In later experiments it was found that the brown impurities could be removed from the mandelic acid by extracting its aqueous solution with approximately one-tenth of its volume of benzene. Only a small relative volume of benzene was used because the optically active forms of mandelic acid appeared to have a higher solubility in benzene than the racemic form. The small loss in activity resulting from this process of purification was similar to that when alumina was used.

The mandelic acid adsorbed on the wool was recovered by immersing the wool fibres in 1 l. of 0·1N-ammonia for an hour at the room temperature. The solution was filtered, evaporated to small volume, acidified, and then extracted three times with twice its volume of ether. The aqueous solution, concentrated to 18 c.c., had α_D = −0·02°.

The ethereal extract, which was pale yellow, was evaporated to dryness and the residue (6·5 g.) dissolved in ethyl alcohol to give 18 c.c. of a solution, having α_D +0·45°, corresponding to $[\alpha]_D$ +0·6°.

The alcoholic solution was evaporated to dryness and the bulk of the residue recrystallised from toluene. The crystals which separated were dissolved in ethyl alcohol to give 17·5 c.c. of solution α_D +0·03°.

The toluene filtrate was evaporated to dryness and the mandelic acid thus recovered was dissolved in ethyl alcohol to give 17·5 c.c. of a solution, α_D +0·40°.

The alcoholic solution was evaporated to dryness and the residual mandelic acid dissolved in cold benzene. The benzene solution was passed through a column of alumina and the brown bands which formed were eluted. The mandelic acid retained on the alumina was recovered by extraction with 3·5% hydrochloric acid. The acid solution was extracted with ether, the ethereal solution evaporated, and the residue recrystallised from a small volume of benzene. The mandelic acid, m. p. 118°, which separated, was dissolved in ethyl alcohol to give 17·5 c.c. of a solution, α_D +0·35°.

The solution containing the brown impurities eluted by means of benzene and acetone was concentrated to 18 c.c., the solution then having α_D +0·02°.

Absorption of Mandelic Acid on Casein.—Casein (40 g.) was added to a solution containing (±)-mandelic acid (15 g.) in absolute alcohol (100 c.c.). After the mixture had been kept for 6 days at the room temperature in a stoppered flask, the casein was filtered off and the filtrate concentrated; its optical rotation was α_D −0·78°. The solution was evaporated, the residue (10·3 g.) extracted by means of ether, and the solute recovered. Its optical rotation in absolute alcohol was α_D −0·58°. The solute, crystallised from toluene, gave mandelic acid, α_D −0·08°. The toluene mother-liquor, chromatographed on alumina, afforded a second crop of mandelic acid, m. p. 118°, having α_D −0·41° in absolute alcohol.

The mandelic acid absorbed by the casein was extracted by immersion for an hour in 0·1N-ammonia. The solution was filtered, and the filtrate acidified, and then extracted by ether. Evaporation of the ethereal extract afforded 3·6 g. of a residue having α_D +0·35°, $[\alpha]_D$ +0·8°. A benzene solution of the residue, chromatographed on alumina, afforded mandelic acid, m. p. 118°, α_D +0·21°.

Action of Weak Acids and Ammonia on Wool.—In a series of experiments wool was left in contact with dilute aqueous solutions of acetic and chloroacetic acids. The solutions became lævorotatory and very little of the optical activity was transferred, when the solutions were extracted by means of ether.

Similar experiments were carried out with dilute aqueous ammonia, the filtered extracts being acidified before being extracted by ether. The results are shown in the table.

Reagent.	Amount.	Amount of wool, g.	Temp.	Time (hrs.).	Fraction of reagent examined.	Optical rotation.* (A.)	(B.)
0·2N-(±)-Mandelic acid	1 l.	60	15°	240	Not absorbed	−0·66°	−0·60°
					Absorbed	—	+0·45
0·2N-Acetic acid	1 l.	60	15	240	Not absorbed	−0·16	−0·01
0·2N-Chloroacetic acid	1 l.	60	15	240	Not absorbed	−0·31	−0·02
0·1N-Ammonia	200 c.c.	20	15	1	Not absorbed	−0·007	—
0·1N-Ammonia	200 c.c.	20	50—60	2	Not absorbed	−0·02	—

* $l = 2$.

(A) Aqueous extract as separated. (B) Aqueous extract extracted by means of ether, the ethereal extract evaporated, and the residue dissolved in water.

The experiment on the absorption of mandelic acid on casein was repeated with benzoic acid (12 g.) instead of (±)-mandelic acid (15 g.). α_D corresponding to (A) in the table was −0·18°, and corresponding (B) −0·02° (not absorbed) and −0·02° (absorbed) ($l = 2$).

Absorption of α-Naphthylglycollic Acid on Wool.—Wool fibres (30 g.) were immersed for 6 days at the room temperature in a solution containing (±)-α-naphthylglycollic acid (8 g.; m. p. 98—99°; prepared from chloral and α-naphthylmagnesium bromide by McKenzie and Dennler's method, *J.*, 1926, 1599), in a mixture of water (500 c.c.) and alcohol (300 c.c.). The unabsorbed acid was recovered (α_D −0·54°) and suspended in water, the suspension shaken with a small volume of benzene, and the undissolved acid recovered (α_D −0·53°). The absorbed acid (4·4 g.), recovered by means of ammonia and purified as for the unabsorbed acid, had α_D +0·50°, $[\alpha]_D$ +1·0°.

In an identical experiment using (±)-mandelic acid (6·0 g.), the unabsorbed acid had α_D −0·35°, and the absorbed acid α_D +0·31°.

In these experiments the rotations were measured in ethyl alcohol.

To estimate the extent of loss of optical activity in dissolution and recovery of mandelic acid, (−)-mandelic acid was submitted to the following process. The acid (5·02 g.), dissolved in ethyl alcohol to give 17·5 c.c. of solution (α_D −1·24°) was recovered by evaporation and dissolved in distilled water (200 c.c.), the solution kept at 90—95° for 6 hours, and the acid recovered by evaporation (5·00 g.) and dissolved in ethyl alcohol to give 17·5 c.c. of solution, which then had α_D −1·22°.

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CLOTHWORKERS RESEARCH LABORATORY,
THE UNIVERSITY, LEEDS.

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107. *Tropolones. Part I. The Preparation and General Characteristics of Tropolone.*

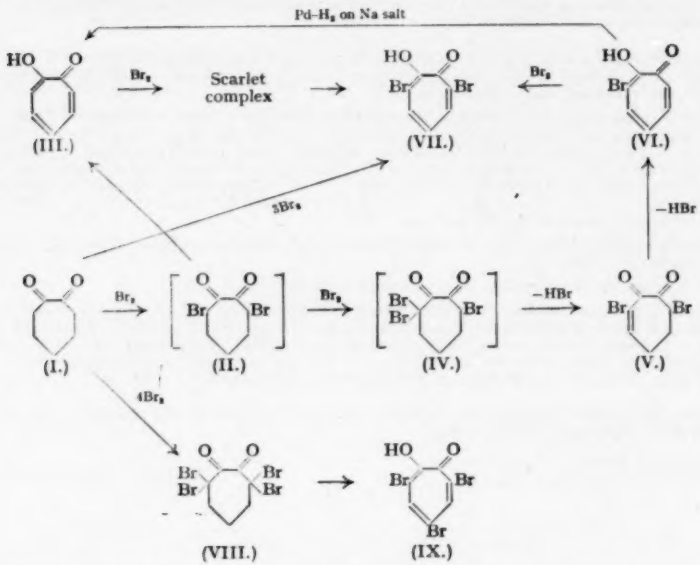
By J. W. COOK, A. R. GIBB, R. A. RAPHAEL, and A. R. SOMERVILLE.

Bromination of *cyclo*heptane-1 : 2-dione in glacial acetic acid with varying proportions of bromine gave a series of bromo-compounds. The inter-relationship of these products is interpreted by a self-consistent reaction scheme. One of them was a bromotropolone; its sparingly soluble sodium salt underwent smooth hydrogenolysis to tropolone which thus becomes readily available for detailed study. Some phases of this are recorded.

THE inspired suggestion of Dewar (*Nature*, 1945, **155**, 50) that the properties of the mould metabolite, stipitatic acid, could be interpreted by assigning to it the structure of a derivative of 2-hydroxy*cyclo*hepta-2 : 4 : 6-trienone (tropolone; III) has attracted widespread interest and has been very fruitful in elucidating the structures of a variety of natural products (cf. Loudon, *Ann. Reports*, 1948, **45**, 187). Tropolone structures have been established for stipitatic acid (Corbett, Johnson, and Todd, *J.*, 1950, 147), puberulic acid (*idem*, *ibid.*, p. 6), α-, β-, and γ-thujaplicin (Erdtman, Gripenberg, and Anderson, *Acta Chem. Scand.*, 1948, **2**, 625, 639, 644), and purpurogallin (Haworth, Moore, and Pauson, *J.*, 1948, 1045). There is also strong, though less conclusive, evidence that colchicine is a tropolone derivative (Loudon,

loc. cit.; Scott and Tarbell, *J. Amer. Chem. Soc.*, 1950, **72**, 240), as suggested by Dewar (*Nature*, 1945, **155**, 142).

By extrapolation of the known properties of these natural products a fairly complete picture may be constructed of the probable chemical attributes of the parent compound of the series, namely, tropolone itself. It was clearly desirable to devise methods of synthesis of tropolone for the dual purpose of providing material for a study of its chemistry and to extend these methods to the synthesis of natural tropolones. The present communication is concerned with the synthesis of tropolone and a general survey of its properties. A preliminary summary of some of this work has already been published (*Chem. and Ind.*, 1950, 427). The results fully confirm Dewar's prediction that the tropolone ring would have aromatic stability.



It was found that the most obvious and direct route to tropolone, *i.e.*, the dehydrogenation of *cyclo*heptane-1 : 2-dione (I) with reagents such as selenium, palladium, or chloranil, could not be used, as the dione resinified under such treatment. Failure of this approach led to the investigation of the natural alternative, the bromination–dehydrobromination of the dione. This reaction proved to be unexpectedly complex, the nature of the products being highly dependent on the proportion of bromine used. The action of one mole of bromine in glacial acetic acid on *cyclo*heptane-1 : 2-dione gave a small yield of a dense oil [presumably 3 : 7-dibromo*cyclo*heptane-1 : 2-dione (II)] which, on dehydrobromination with sodium hydroxide solution, furnished tropolone (III) by way of its sodium salt. This procedure was attended by the formation of much tar, and the method cannot be regarded as preparative. When the dione was treated in glacial acetic acid with two moles of bromine and then heated for a short period, hydrogen bromide was profusely evolved and a sparingly soluble, crystalline compound separated. This did not possess tropolone-like properties, and analysis indicated its formula to be compatible with the structure (V) formed by the elimination of one mole of hydrogen bromide from the intermediate 3 : 3 : 7-tribromo*cyclo*heptane-1 : 2-dione (IV). Compound (V) was unstable and slowly evolved hydrogen bromide when kept. This elimination was rapid and quantitative when (V) was warmed with sodium hydroxide solution: dissolution rapidly occurred and the resulting deep yellow solution, on being cooled, deposited the sparingly soluble, highly crystalline sodium salt of bromotropolone (VI); the overall yield of the pure sodium salt based on the starting dione was 26%. If the intermediate compound (V) was not isolated, but heated further in the acetic acid reaction medium, it slowly dissolved with evolution of hydrogen bromide; cooling resulted in the crystallisation of bromotropolone

(VI) itself. This procedure, however, gave an inferior yield. On being shaken with hydrogen in the presence of a palladium–charcoal catalyst, the sodium salt of bromotropolone (VI) underwent smooth hydrogenolysis to give tropolone in 78% yield, the reaction ceasing after the absorption of one mole of hydrogen. The convenience and ease of this series of reactions render attainable relatively large amounts of tropolone for the detailed investigation of its physical and chemical properties. Recently, two further syntheses of tropolone have been described. The first consists of the permanganate oxidation of *cyclo*hepta-1 : 3 : 5-triene, itself prepared by photochemical diazomethane ring-expansion of benzene (Doering and Knox, *J. Amer. Chem. Soc.*, 1950, **72**, 2305), whereas the second involves the stepwise degradation of purpurogallin (Haworth and Hobson, *Chem. and Ind.*, 1950, 441). It seems unlikely that either of these procedures could be utilised on a preparative scale.

It might be supposed that the formation of bromotropolone (VI) could be more simply interpreted as the further bromination of initially formed tropolone. This explanation is untenable in view of the fact that bromination of tropolone under analogous conditions does not give bromotropolone (VI); as will be described more fully in a future communication, a scarlet complex is first formed which disproportionates into tropolone and dibromotropolone (VII).

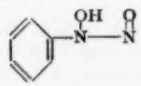
The bromination of *cyclo*heptane-1 : 2-dione in glacial acetic acid with three moles of bromine led to the formation of a dibromotropolone (VII), m. p. 157—158°. The production of this compound may be satisfactorily explained as the further bromination of pre-formed bromotropolone (VI), a reaction which has been confirmed experimentally. Hydrogenolysis of the sodium salt of this dibromotropolone did not give the expected monobromotropolone, but a mixture of equal amounts of tropolone and dibromotropolone; addition of a further mole of sodium hydroxide and continuation of the hydrogenolysis led to complete debromination and conversion into tropolone. When the dione (I) was treated with four moles of bromine in the cold, no tropolone-like material was obtained, the only isolable product consisting of 3 : 3 : 7 : 7-tetrabromo*cyclo*heptane-1 : 2-dione (VIII), m. p. 84°. Attempts to dehydrobrominate this compound by means of sodium hydroxide solution or pyridine led only to tar formation. On being heated to 130°, the tetrabromo-compound evolved hydrogen bromide; the product, purified through its sodium salt, was found to be a tribromotropolone (IX), m. p. 123°. It is difficult to formulate a rational mechanism for the production of (IX) from (VIII) and the exact course of the reaction remains obscure.

The production and inter-relationship of these compounds may be satisfactorily interpreted by the above reaction scheme, but it should be emphasised that the structures assigned, although likely, are tentative and their confirmation, or otherwise, must await the results of orientation investigations which are now in progress. The above products are always more highly brominated than would seem to be compatible with the corresponding molar proportions of bromine employed in the reaction, *e.g.*, the dione (I) gives bromotropolone (VI) *via* (V) and (IV) by the use of only two instead of the expected three moles of bromine. This apparent anomaly is probably due to the fact that the dione (I) is an unstable compound which always undergoes some unproductive degradation during bromination. The true bromine : dione ratio of the reaction mixtures is therefore considerably higher than that indicated by the actual initial weights of the reactants.

The above procedure is obviously applicable to the preparation of substituted tropolones, and indeed application of the method to the relevant homologous diones has resulted in the synthesis of three naturally occurring tropolones, the α-, β- and γ-thujaplicins (forthcoming publication).

Tropolone crystallised from light petroleum in long, almost colourless needles, m. p. 49—50°, possessing a remarkably high vapour pressure, as volatilisation occurred readily at room temperature. If exposed at room temperature to the atmosphere, tropolone slowly coloured and became sticky, but it could be kept indefinitely without apparent change at temperatures below 0°. It was readily soluble in water and organic solvents. It dissolved rapidly in sodium hydrogen carbonate solution with effervescence and the production of the yellow sodium salt; electrometric titration with sodium hydroxide solution indicated a pK value of 7·00 ± 0·02 at 20° which is midway between the values obtained for a typical phenol (*e.g.*, pK 10·0 for phenol itself) and a simple carboxylic acid (pK 4·8 for acetic acid). With ferric chloride solution tropolone in aqueous solution gave an intense deep green colour. This colour reaction took place in two distinct stages: if a limited amount of ferric chloride was used a red precipitate was first formed; this redissolved on further addition of ferric chloride to form the deep green solution. The red solid was readily soluble in chloroform, from which it crystallised in reddish-black needles; analysis showed that these consisted of ferric tropolone. The ready formation

of this compound and the intense colour of its extremely dilute solutions in chloroform suggests its use for the colorimetric estimation of ferric ion. Similarly, treatment of tropolone with aqueous solutions of cupric and cuprammonium salts resulted in the formation of the chloroform-soluble cupric complex which readily crystallised from many organic solvents. In contradistinction to sodium tropolone, which behaved as a true ionised salt, the ferric and cupric compounds showed the properties of typical co-ordination complexes. This reaction of tropolone with cupric and ferric ions recalls the analogous behaviour of the well-known analytical reagent cupferron (X) and some formal resemblance is indeed apparent between the structures of the two compounds.

(X.)  (III.)

No carbonyl reactions or ketonic derivatives could be obtained from any of the above tropolones; thus the action of semicarbazide acetate, hydroxylamine acetate, and 2 : 4-dinitrophenylhydrazine sulphate left the compounds unchanged; moreover, treatment with *o*-phenylenediamine did not result in quinoxaline formation. The preparation, from the tropolones, of derivatives involving the hydroxyl group was unexpectedly troublesome; solid acetates could not be obtained and attempts to prepare, by standard procedures, the *p*-nitrobenzyl, 2 : 4-dinitrophenyl, and carboxymethyl ethers were fruitless. *S*-Benzylthiuronium and benzylamine salts were readily formed, but rapidly broke up into their constituents on attempted purification. 3 : 5-Dinitrobenzoates were obtainable, however, and treatment of the tropolones with diazomethane and diphenyldiazomethane gave respectively the crystalline methyl and diphenylmethyl ethers. As with the parent compounds these ethers did not exhibit carbonyl reactivity.

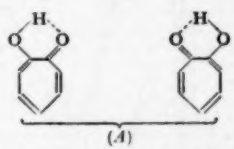
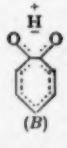
No reaction took place on attempted catalytic hydrogenation of tropolone when palladium was employed as catalyst, thus providing some indication that the double bonds in the compound are not of the ordinary ethylenic type. The action of tetranitromethane in petroleum gave only a light yellow colour. When platinum was employed as catalyst in the hydrogenation a ready uptake of three moles of hydrogen occurred, followed by a much slower absorption of a further one mole. It is logical to suppose that the first stage leads to the formation of 2-hydroxy-*cyclo*heptanone which is then slowly reduced to a mixture of *cis*- and *trans-cyclo*heptane-1 : 2-diol; this reluctance of cyclic α-ketols (acyloins) to undergo hydrogenation has been noted before (Stoll *et al.*, *Helv. Chim. Acta*, 1947, **30**, 1820, 1828). Oxidative fission of the hydrogenation product with potassium permanganate gave pimelic acid; thus the presence of a seven-membered carbocyclic ring in tropolone was confirmed. Lithium aluminium hydride reduction of tropolone has as yet given no pure chemical entity as product.

It was obviously of interest to subject tropolone and its methyl ether to those reactions which involve the tropolone ring of colchiceine and its methyl ether, colchicine, in order to examine the degree of correspondence of properties. There is a marked superficial resemblance between the two systems; thus colchiceine gives a green ferric chloride colour, exhibits acidic properties, forms a chloroform-soluble copper salt, and shows no carbonyl reactivity. Further, tropolone methyl ether was far more soluble in water than tropolone, a surprising property exactly paralleled by colchicine and colchiceine. In contrast, however, there seems to be far less tendency for tropolone and its methyl ether to rearrange into benzenoid derivatives than is exhibited by colchiceine and colchicine. Thus colchicine on treatment with methanolic sodium methoxide is smoothly converted into *allo*colchicine, the tropolone-like ring undergoing contraction to form the methyl ester of a substituted benzoic acid (Fernholz, *Annalen*, 1950, **568**, 66; cf. Šantavý, *Helv. Chim. Acta*, 1948, **31**, 821); tropolone methyl ether was unaffected by sodium methoxide under the same conditions. Other naturally occurring tropolones (*e.g.*, γ-thujaplicin, stipitatic acid, purpurogallin) undergo a similar transformation into substituted benzoic acids on being heated to high temperatures with potassium hydroxide. Heating tropolone with potassium hydroxide at temperatures ranging from 180° to 250° left it to some degree unaltered and no benzoic acid could be isolated. Oxidation of colchiceine with alkaline hydrogen peroxide converts the tropolone ring into a phenolic ring with formation of *N*-acetylcolchinol (Čech and Šantavý, *Coll. Czech. Chem. Comm.*, 1949, **14**, 532); tropolone was practically unaffected by this reagent although a small quantity of *cis* : *cis*-muconic acid could be isolated. The latter product was presumably formed by further oxidation of the primary fission product,

cis : *cis*-penta-1 : 3-diene-1 : 5-dicarboxylic acid; a similar oxidation of the *trans* : *trans*-isomer of the diene-acid to *trans* : *trans*-muconic acid has been recorded (Grundmann, *Ber.*, 1937, **70**, 1150). Another means of aromatisation of colchiceine was described by Windaus (*Sitzungsber. Heidelberg. Akad. Wiss., Math.-Nat. Kl., A.*, 1914, 18 Abh.; 1919, 16 Abh.) who found that it underwent conversion into the iodophenol, *N*-acetyliodocolchinol, when treated with cold sodium hypoiodite. Similar treatment of tropolone produced a compound which differed from all of the known iodinated derivatives of phenol; as will be described in a later communication, it exhibited typical tropolone properties and was presumably an iodotropolone. Tropolone coupled readily with *p*-toluenediazonium chloride, giving a red-brown dye; this reaction takes place with many of the naturally-occurring tropolones, but not with colchiceine, which gives only a faint brownish colour.

Heating of tropolone with maleic anhydride or *cyclo*pentadiene furnished no adduct.

The question of the fine structure of the tropolone ring system is obviously of fundamental interest from the theoretical standpoint, and purely chemical investigations can clearly contribute in only a limited degree to the solution of the problem. Chemical studies have therefore been supplemented by some of the modern physico-chemical techniques. As a first approximation the structure of tropolone may be written as

either  or 

(*A*) (*B*)

where the two equivalent forms of (*A*) are to be regarded as tautomers involving rapid interchange rather than as extreme canonical forms of a true electronic resonance hybrid such as the alternative ionic " benzenoid " formulation (*B*). The infra-red absorption properties of tropolone and its derivatives would obviously provide crucial data for discrimination between the two concepts, and the required investigation has been carried out by Dr. Koch, whose results and the deductions therefrom are described fully in the following paper; it may be stated here that the spectroscopic evidence rules out the possibility of electronic resonance degeneracy involving two equivalent bonds between the proton and the two oxygen atoms, as in (*B*), and points with a strong degree of probability to a structure such as (*A*) for tropolone in which the hydroxylic hydrogen atom is regarded as being symmetrically located *on a time average basis* between the two oxygen atoms which will thus become chemically equivalent. It should be pointed out that the structure of salts of tropolone may well differ in their degree of attaining complete " benzenoid " resonance degeneracy.

The calculated resonance energy of tropolone based on this model is seen from the following paper to be in excellent agreement with that found experimentally. The thermochemical data for the computation of the latter value were very kindly provided by Dr. G. R. Nicholson of the Dyestuffs Division of Imperial Chemical Industries Limited. He has determined the standard heat of combustion of tropolone (at 25° and 1 atmosphere pressure), ΔH_c, to be $-806{\cdot}2 \pm 0{\cdot}9$ kcals./mole and the heat of sublimation at 25°, ΔH_s, to be $+20{\cdot}0 \pm 0{\cdot}2$ kcals./mole. From the first of these results the heat of combustion of tropolone (solid) may be deduced as $-57{\cdot}1$ kcals./mole and thence, by use of the heat of sublimation, the heat of combustion of tropolone (gaseous) at 25° is found to be $-37{\cdot}1$ kcals./mole. Hence, by use of the heats of atomisation C 126·3, H 51·71, and O 58·9 kcals./g.-atom, the heat of formation of gaseous tropolone from its elements in their gaseous atomic states is found to be $-1349{\cdot}3$ kcals./mole. By means of the relevant bond energies (as given by Coates and Sutton, *J.*, 1948, 1187) the energy of the formal chemical bonds in tropolone may be calculated as 1320·7 kcals./mole. The difference between these experimental and theoretical values, *i.e.*, the resonance energy of tropolone, is thus seen to be 28·6 kcals./mole.

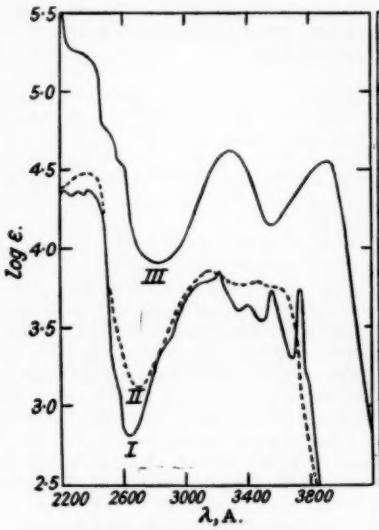
The ultra-violet absorption spectra of tropolone and its derivatives are consistent with the above concept of the fine structure. Thus the close similarity between the absorption curves of tropolone and its methyl ether (Fig. 2) would appear to tell against any formulation of tropolone as a true resonance hybrid of type (*B*). The absorption curve of tropolone in sodium hydroxide solution (Fig. 1), *i.e.*, that of the yellow tropolone anion, is seen, however, to be markedly different; this indicates a radical change of structure in the ion which may plausibly be attributed to its existence as a " benzenoid " resonance hybrid. Copper tropolone,

whose properties are those of a typical co-ordination complex in contrast to the undoubtedly strongly ionised sodium salt, exhibits an absorption (Fig. 2) different again from the above derivatives. The ultra-violet absorption curves of the brominated tropolones are similar in shape to that of tropolone itself, although the corresponding maxima occur at longer wavelengths.

Detailed *X*-ray crystallographic analysis of tropolone and its derivatives would obviously provide much vital information (*e.g.*, bond lengths) bearing on the fine structure of tropolone, and such investigations are now being carried out by Professor J. M. Robertson and his collaborators.

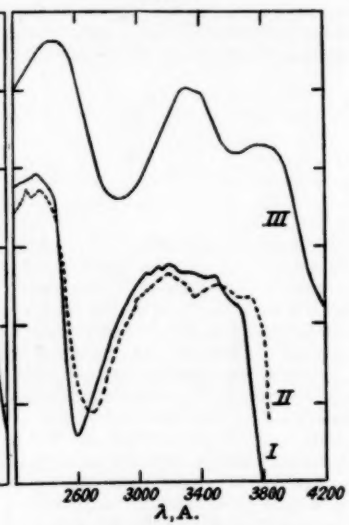
The tropolone structure may be regarded formally as a vinylogue of a carboxyl group and this concept would appear to be endowed with a modicum of reality if comparison be made between the resonance energy of simple carboxylic acids (~25 kcals., to which must be added

FIG. 1.



I. Tropolone in cyclo*hexane.*
II. Tropolone in water.
* *III. Tropolone in* 0·5N-NaOH.

FIG. 2.



I. Tropolone methyl ether in ethanol.
II. Tropolone in ethanol.
* *III. Cupric tropolone in ethanol*

* *To avoid confusion 0·5 unit has been added to the ordinates of these curves.*

an increment of ~6 kcals. contributed by the presence of the conjugated *cyclo*heptatriene system; cf. Wheland, " The Theory of Resonance " pp. 56—58, 69) and tropolone (28·6 kcals.). Further, Dr. Nicholson has suggested that the rather high value for the latent heat of sublimation of tropolone may indicate that the hydrogen bonds are between groups in neighbouring molecules and not within the molecule, thus giving rise to a structure analogous to the well-established hydrogen bond dimers of carboxylic acids. However, the value for the molecular weight of tropolone as determined by ebullioscopic and cryoscopic methods is that expected for the monomer, thus providing evidence that the hydrogen bonding is intra- rather than inter-molecular. Again, neither the C=O nor the O–H characteristic frequencies displayed in the infra-red absorption of tropolone are close to those normally encountered in solid carboxylic acids. A further argument against this vinylogy postulate arises from the fact that compounds such as 3-methyl*cyclo*pent-3-ene-1 : 2-dione (Dane *et al.*, *Annalen*, **1937**, **532**, 29; **1938**, **536**, 196; **1938**, **537**, 246; Stork and Singh, *Nature*, **1950**, **165**, 816) and the many *cyclo*pentane-1 : 2 : 4-triones do not possess tropolone properties although they may be formally regarded as lower vinylogues of tropolone and hydroxytropolone respectively; these compounds behave as typical α-diketones, forming carbonyl derivatives and quinoxalines with great ease.

The marked antifungal properties exhibited by γ-thujaplicin and 3 : 4-benzotropolone (Baillie, Freeman, Cook, and Somerville, *Nature*, 1950, **166**, 65) suggested the examination in this respect of the tropolones obtained as above. Dr. G. G. Freeman and Mr. A. J. Baillie of the Nobel Division of Imperial Chemical Industries Limited have tested the fungistatic and bacteriostatic activity of the compounds against seven fungal species and four test bacteria at concentrations of 80—0·6 mg./l. The organisms were inoculated on to Petri dishes containing nutrient medium including the tested concentration of the compounds. Growth of the fungi was read after 5 days at 25° and growth of bacteria after 2 days at 35°. Tropolone, bromotropolone (VI), and dibromotropolone (VII) showed slight fungistatic and bacteriostatic activity at 80 mg./l., and no significant activity at 16 mg./l. In view of the low fungistatic activity no fungicidal tests were carried out.

Experimental.

*cyclo*Heptanone was prepared by the diazomethane ring expansion of *cyclo*hexanone (Kohler, Tishler, Potter, and Thomson, *J. Amer. Chem. Soc.*, 1939, **61**, 1057). From the former ketone *cyclo*heptane-1 : 2-dione was obtained by selenium dioxide oxidation (Vanderhaar, Voter, and Banks, *J. Org. Chem.*, 1949, **14**, 836).

Bromination of cyclo*Heptane*-1 : 2-*dione*.—(a) *Reaction with one mole of bromine.* To a cooled (0°) and stirred solution of *cyclo*heptane-1 : 2-dione (10 g.) in glacial acetic acid (10 c.c.) was added dropwise, during 15 minutes, bromine (12·8 g.) in glacial acetic acid (10 c.c.). After 1 hour the reaction mixture was heated by steam until the evolution of hydrogen bromide ceased (*ca.* 1 hour). It was then distilled in steam, and the distillate (800 c.c.) made alkaline with solid sodium carbonate and extracted with ether. Drying and evaporation of this extract furnished a brown oil; this did not exhibit tropolone-like properties but, on being warmed with sodium hydroxide solution (5N.), it rapidly dissolved to give a yellow solution. Acidification (2N-sulphuric acid) and isolation by means of ether furnished impure tropolone as a gum from which pure tropolone sublimed on heating. Further small quantities could be obtained by acidification of the alkaline steam-distillation mother-liquor and by alkali treatment of the tarry non-volatile residue. The total yield of tropolone by this procedure was 1·4 g. (15%).

(b) *Reaction with two moles of bromine.* To a cooled (0°) and stirred solution of the dione (200 g.) in glacial acetic acid (200 c.c.) was added dropwise, during 4 hours, a solution of bromine (520 g.) in glacial acetic acid (200 c.c.), and the reaction mixture set aside at room temperature for 16 hours. The resulting dark orange solution was then heated by steam for 20 minutes; hydrogen bromide was profusely evolved and a dense, crystalline solid (130 g.) was precipitated, which, after being cooled, was filtered off, washed with a little cold acetic acid, and dried on porous tile. This compound could be crystallised rapidly from acetic acid but its instability precluded an accurate analysis; it slowly evolved hydrogen bromide even at room temperature. The bromine analysis, which indicated the presence of two atoms of bromine for each *cyclo*heptane nucleus, and its general properties, were in harmony with the structure (V) (Found : Br, 53·7. Calc. for $C_7H_4O_3Br_2$: Br, 56·7%). This product was then heated with excess of sodium hydroxide solution until completely dissolved (*ca.* 4 l. of 6N-sodium hydroxide are needed) and the resulting yellowish-brown solution cooled to 0°. The separated crystalline mass was filtered off and washed with a little cold brine. A further small quantity of product was obtained by steam-distillation of the acetic acid mother-liquor and extraction of the tarry residue with hot sodium hydroxide solution. The combined product was crystallised from aqueous alcohol (75%) from which the sodium salt of bromotropolone (107 g., 26%) crystallised as the *dihydrate* in lustrous, deep yellow plates, m. p. 308° (decomp.) (Found : C, 32·65; H, 2·9. $C_7H_4O_3BrNa,2H_2O$ requires C, 32·7; H, 3·1%). Dehydration of the *salt* was accomplished by heating it at 100° *in vacuo* for some time; analysis of the dried material indicated a tenacious retention of a small proportion of water (Found : C, 36·7; H, 1·6. $C_7H_4O_3BrNa$ requires C, 37·7; H, 1·8%).

Acidification (2N-sulphuric acid) of an aqueous solution of this sodium salt caused the precipitation of *bromotropolone* (VI) itself, which could be obtained in polymorphic forms. Crystallisation from aqueous acetic acid gave pale green nacreous plates, whereas the compound separated from *cyclo*hexane in cream-coloured needles, which, when kept, changed to pale yellowish-green polyhedra; all these forms had m. p. 103—106° (Found : C, 41·75; H, 2·6; Br, 39·9. $C_7H_5O_3Br$ requires C, 41·8; H, 2·5; Br, 39·75%). Light absorption in ethanol : $\lambda_{max.}$ 2520, 2570, 3270, 3680, 3800 A.; log ε = 4·47, 4·48, 3·82, 3·76, 3·72. $\lambda_{infl.}$, 2330, 3180, 3860 A.; log ε = 4·14, 3·76, 3·60. Bromotropolone was also prepared by heating the originally obtained suspension of the intermediate compound (V) in acetic acid until no further evolution of hydrogen bromide was apparent and all the solid had dissolved; cooling to 0° caused the separation of bromotropolone. This procedure, however, favoured the formation of tarry by-products, and the yield was correspondingly reduced. Conversion of the intermediate (V) directly into bromotropolone was accomplished by warming it with aqueous methanol; dissolution rapidly occurred and the product separated on cooling.

Bromotropolone dissolved in sodium hydrogen carbonate solution with effervescence giving a yellow solution; with ferric chloride a deep green colour was immediately formed. The bromine atom in (VI) was very firmly bound; the compound was recovered unchanged after treatment with hot alcoholic potassium hydroxide, and alcoholic silver nitrate gave only the bright yellow, unstable silver salt decomposing vigorously at 178°. With cuprammonium sulphate solution an aqueous solution of sodium bromotropolone gave the corresponding *cupric* salt, which crystallised from tetrachloroethane as an infusible, light green powder (Found : C, 36·4; H, 1·75. $C_{14}H_6O_4Br_2Cu$ requires C, 36·4; H, 1·75%).

Bromotropolone reacted with ethereal diazomethane to give the *methyl ether*, which crystallised from light petroleum (b. p. 80—100°) in needles, m. p. 89—90° (Found : C, 44·7; H, 3·5; OMe, 14·0.

$C_8H_7O_3Br$ requires C, 44·7; H, 3·3; OMe, 14·4%). Light absorption in ethanol: $\lambda_{max.}$, 2540, 3270, 3610 A.; log ε = 4·63, 3·90, 3·87. $\lambda_{infl.}$, 3120, 3740 A.; log ε = 3·82, 3·77. The **3 : 5-*dinitrobenzoate***, obtained by the usual procedure, formed stout needles, m. p. 105—106°, from benzene–light petroleum (b. p. 60—80°) (Found: C, 42·8; H, 2·1. $C_{14}H_7O_7N_2Br$ requires C, 42·55; H, 1·8%). These homogeneous derivatives were unaccompanied by the position isomers which are theoretically possible.

(c) *Reaction with three moles of bromine* (by G. L. BUCHANAN). To a cooled (0°) and stirred solution of the dione (20 g.) in glacial acetic acid (20 c.c.) was added dropwise, during 20 minutes, a solution of bromine (78 g.) in glacial acetic acid (80 c.c.). After 2 hours at room temperature the dark solution was heated by steam until the evolution of hydrogen bromide ceased, and then evaporated under reduced pressure to half its bulk. On being cooled to 0°, the reaction mixture deposited a crystalline mass of ***dibromotropolone*** (VII) (13·5 g.), crystallising from alcohol or toluene in cream-coloured needles, m. p. 157—158° (Found: C, 30·2; H, 1·45; Br, 57·6. $C_7H_4O_3Br_2$ requires C, 30·0; H, 1·45; Br, 57·1%). Light absorption in ethanol: $\lambda_{max.}$, 2640, 3350, 3730, 3890 A.; log ε = 4·44, 3·77, 3·64, 3·71. $\lambda_{infl.}$, 3190, 4230 A.; log ε = 3·64, 2·66. The compound gave a deep green ferric chloride colour in alcohol. It dissolved with effervescence in warm aqueous sodium carbonate, to give a yellow solution of the sparingly soluble *sodium* salt, which crystallised from hot water in yellow needles, m. p. 296° (decomp.) (Found: C, 28·0; H, 1·1. $C_7H_3O_3Br_2Na$ requires C, 27·85; H, 1·0%). Action of ethereal diazomethane on dibromotropolone gave the ***methyl ether***, crystallising from toluene–light petroleum (b. p. 100—120°) in colourless needles, m. p. 130—131° (Found: C, 33·0; H, 2·15; OMe, 10·85. $C_8H_6O_3Br_2$ requires C, 32·7; H, 2·05; OMe, 10·55%). Light absorption in ethanol: $\lambda_{max.}$, 2660, 3360 A.; log ε = 4·38, 3·77.

(d) *Reaction with four moles of bromine.* To a cooled (0°) stirred solution of the dione (5 g.) in glacial acetic acid (20 c.c.), bromine (25 g.) was rapidly added. After 1 hour at room temperature the solution was poured into water; the precipitated oil slowly solidified and crystallisation from aqueous acetic acid and then from benzene–light petroleum (b. p. 60—80°) gave **3 : 3 : 7 : 7-*tetrabromocycloheptane*-1 : 2-*dione*** (VIII) (3·5 g.) as colourless plates, m. p. 82—84° (Found: C, 18·5; H, 1·75; Br, 72·2. $C_7H_4O_2Br_4$ requires C, 19·0; H, 1·35; Br, 72·4%). The product gave no colour with ferric chloride, and warming with sodium hydroxide solution and pyridine produced tars. On being heated to 130°, however, (VIII) rapidly evolved hydrogen bromide, to give a product which dissolved in hot sodium hydroxide solution to form a deep yellow solution. On cooling, this deposited a yellow sodium salt. Acidification of the salt, followed by crystallisation of the product from a small volume of alcohol, gave ***tribromotropolone*** (IX) as pale yellow needles, m. p. 122—123° (Found: C, 23·7; H, 1·1; Br, 66·5. $C_7H_3O_2Br_3$ requires C, 23·45; H, 0·85; Br, 66·8%). Light absorption in ethanol: $\lambda_{max.}$, 2580, 2710, 3500, 4400 A.; log ε = 4·85, 4·85, 4·38, 4·09. An alcoholic solution of the compound gave a deep green colour with ferric chloride!

In another experiment the dione (10 g.), glacial acetic acid (30 c.c.), and bromine (54 g.) were heated by steam until no further hydrogen bromide evolution occurred, and the reaction mixture was taken to dryness under reduced pressure. The dark red, viscous residue did not give a colour with ferric chloride and did not dissolve in warm alkali. On being heated to 130°, the material briskly evolved hydrogen bromide, and hot sodium hydroxide solution extracted from the product the sodium salt of tribromotropolone (1·7 g.) which was converted into the parent compound as described above.

Tropolone (III).—A suspension of finely-powdered sodium bromotropolone dihydrate (25 g.) in alcohol (200 c.c.) was stirred under hydrogen in the presence of palladium–charcoal (2·5 g.; 10%). The smooth absorption of hydrogen ceased after the uptake of 1 mole (3 hours). The cherry-red filtrate was evaporated under reduced pressure (temperature $\gtrsim$40°) and the residue extracted with boiling light petroleum (b. p. 40—60°). On being cooled to −10° the extract deposited long, cream-coloured needles of ***tropolone*** (9·8 g., 78%) [Found: C, 68·75; H, 4·8; neutr. equiv., 126; *M* (ebullioscopic in acetone), 125, (cryoscopic in benzene), 126. $C_7H_6O_2$ requires C, 68·85; H, 4·95%; *M*, 122·1]. Light absorption: In *cyclo*hexane (Fig. 1): $\lambda_{max.}$, 2220, 2320, 2380, 3220, 3400, 3560, 3740 A.; log ε = 4·37, 4·36, 4·37, 3·84, 3·64, 3·73, 3·74; $\lambda_{infl.}$, 2840, 3070 A.; log ε = 3·34, 3·77. In ethanol (Fig. 2): $\lambda_{max.}$, 2280, 2370, 3200, 3510 A.; log ε = 4·36, 4·36, 3·83, 3·76; $\lambda_{infl.}$, 3030, 3710 A.; log ε = 3·70, 3·68. In water (Fig. 1): $\lambda_{max.}$, 2380, 3160, 3470 A.; log ε = 4·48, 3·86, 3·79; $\lambda_{infl.}$, 3620 A.; log ε = 3·75. In 0·5N-sodium hydroxide (Fig. 1): $\lambda_{max.}$, 3290, 3920 A.; log ε = 4·12, 4·05; $\lambda_{infl.}$, 2400, 2340, 2590 A.; log ε = 4·70, 4·21, 4·04. The compound was highly volatile and could be sublimed with great ease; it was readily soluble in all the common organic solvents and in water, and dissolved with effervescence in sodium hydrogen carbonate solution to give the very soluble yellow sodium salt. With excess of ferric chloride solution tropolone gave an intense deep green colour, but with a limited amount of the reagent the red, insoluble *ferric tropolone* was precipitated; this compound crystallised from chloroform–carbon tetrachloride in lustrous, intensely red needles which did not melt or decompose below 360°. Sparingly soluble in water and most organic solvents, it dissolved readily in chloroform (Found: C, 60·1; H, 3·7. $C_{21}H_{15}O_6Fe$ requires C, 60·15; H, 3·6%). It is the presence of a few mg. of this compound that imparts the red colour to the solution during the preparation of tropolone; it may be extracted from the residue of sodium bromide by chloroform. Its formation is probably due to a trace of iron in the charcoal. Treatment of tropolone with cupric or cuprammonium salt solutions gave an immediate green precipitate, sparingly soluble in most organic solvents, but very soluble in chloroform. This *copper* chelate compound crystallised well from benzene or alcohol in lustrous green needles, decomposing at 300° (Found: C, 55·5; H, 3·25. $C_{14}H_{10}O_4Cu$ requires C, 55·0; H, 3·30%). Light absorption in ethanol (Fig. 2): $\lambda_{max.}$, 2470, 3310, 3800 A.; log ε = 4·82, 4·51, 4·14; $\lambda_{infl.}$, 3400 A.; log ε = 4·48.

Tropolone reacted briskly with ethereal diazomethane, to give a quantitative yield of the *methyl ether*, which crystallised from ether or carbon tetrachloride as its hemihydrate, prismatic needles, m. p. 37—38° (Found: C, 66·5; H, 6·1; OMe, 21·8. $C_8H_8O_2,0·5H_2O$ requires C, 66·2; H, 6·25; OMe, 21·4%). Light absorption in ethanol (Fig. 2): $\lambda_{max.}$, 2350, 3140, 3190, 3500 A.; log ε = 4·46, 3·87, 3·88, 3·81; $\lambda_{infl.}$, 3060, 3360, 3630 A.; log ε = 3·83, 3·83, 3·64. The water of crystallisation was

removed under reduced pressure over silica gel, yielding the anhydrous ether as an oil; analysis of this oil was not possible owing to its extremely rapid reaction with atmospheric moisture to re-form the crystalline hemihydrate. The methyl ether was rapidly reconverted into tropolone on being warmed with 2N-sulphuric acid. The *picrate* of the methyl ether crystallised from methanol in yellow needles, m. p. 119—120° (Found: C, 45·8; H, 3·25. $C_8H_8O_2,C_6H_3O_7N_3$ requires C, 46·05; H, 3·05%). The *diphenylmethyl ether*, prepared by heating tropolone with a benzene solution of diphenyldiazomethane (Hardegger, El Heweihi, and Robinet, *Helv. Chim. Acta*, 1948, **31**, 439), crystallised from light petroleum (b. p. 100—120°) in rosettes, m. p. 142—143° (Found: C, 83·4; H, 5·6. $C_{20}H_{14}O_2$ requires C, 83·4; H, 5·6%). *Tropolone* 3 : 5-*dinitrobenzoate*, prepared by the standard method in poor yield, formed prismatic plates, m. p. 169—171°, from toluene–light petroleum (b. p. 100—120°) (Found: C, 53·6; H, 2·75. $C_{14}H_8O_7N_2$ requires C, 53·15; H, 2·55%). Treatment of an alkaline solution of tropolone with excess of *p*-toluenediazonium chloride solution resulted in the precipitation of *p-tolylazotropolone*, which crystallised from ethanol as a reddish-brown microcrystalline powder, sintering at 140° and finally melting at 190—193° (Found: N, 12·0. $C_{14}H_{12}O_2N_2$ requires N, 11·65%). An alcoholic solution of the azo-compound gave a green colour with ferric chloride and a deep green copper salt with copper sulphate solution.

Hydrogenation of Tropolone.—A solution of tropolone (160 mg.) in alcohol (25 c.c.) was stirred under hydrogen in the presence of pre-reduced platinum (from platinic oxide, 100 mg.). Three moles of hydrogen were absorbed rapidly (30 minutes); the rate of uptake then suddenly changed and absorption of the fourth mole of hydrogen was only complete after 3 hours. Removal of catalyst and solvent gave a thick oil which hardened to a waxy solid at −15°. To an emulsion of the oil in water (10 c.c.) and sodium carbonate solution (2 c.c.; 2N.) was slowly added powdered potassium permanganate (200 mg.). After 10 minutes the mixture was acidified to Congo-red with 2N-sulphuric acid, and sulphur dioxide was passed in until the solution was clear. The reaction mixture was shaken with ether, and the acidic product extracted into sodium carbonate solution and finally isolated by acidification and ether-extraction. Drying ($MgSO_4$) and evaporation gave a solid residue (125 mg.), crystallising from benzene in small needles, m. p. 99—101° undepressed on admixture with authentic pimelic acid.

Hydrogenolysis of Sodium Dibromotropolone.—A suspension of sodium dibromotropolone (1 g.) in alcohol (50 c.c.) was stirred under hydrogen in the presence of palladium–charcoal (200 mg.; 10%). Absorption of hydrogen was very slow and finally ceased after the uptake of 1 mole. It restarted when sodium hydroxide solution (1 mole of N.) was added to the reaction mixture and a further mole of hydrogen was absorbed. Removal of catalyst and solvent, and extraction of the residue with light petroleum (b. p. 40—60°), gave tropolone (360 mg.) identical with that prepared as above. When the reaction mixture was worked up after the absorption of 1 mole of hydrogen, the product consisted of a mixture of tropolone and unchanged dibromotropolone, separated by crystallisation from light petroleum; no monobromotropolone was encountered.

Attempted Conversion of Tropolone and its Methyl Ether into Benzenoid Compounds.—(*a*) To a solution of tropolone (50 mg.) in water (*ca.* 0·5 c.c.) was added solid potassium hydroxide (500 mg.), and the mixture heated to 180° in a metal-bath for 15 minutes. The light brown melt was dissolved in water, acidified, and cooled. As no solid was deposited, the solution was extracted with ether; drying followed by evaporation yielded a brown gum which gave a strong green colour with ferric chloride. Extraction with light petroleum (b. p. 40—60°) gave a small amount (*ca.* 10 mg.) of unchanged tropolone, leaving a small residue of brown resin. Similar results were obtained at temperatures ranging from 180° to 250°.

(*b*) A solution of tropolone (244 mg.) in sodium hydroxide solution (5 c.c. of N.) was treated with hydrogen peroxide (1 c.c.; 30%) and set aside in the dark for 48 hours. No colour change from the original yellow took place. The solution was acidified (2N-sulphuric acid) to Congo-red and extracted with ether. The oily residue obtained by drying and evaporation was extracted with *cyclo*hexane; the extract on cooling deposited needles of unchanged tropolone (180 mg.). The hydrocarbon-insoluble residue (*ca.* 10 mg.) consisted of an acidic solid which was purified by dissolution in sodium carbonate and precipitation by acid; it then melted at 182—184° undepressed on admixture with authentic *cis* : *cis*-muconic acid (cf. Elvidge, Linstead, Sims, and Orkin, *J.*, 1950, 2235).

When the oxidation was carried out in the presence of light the fission product had m. p. 154—162°. A similar m. p. range for *cis* : *cis*-muconic acid prepared in the light has been noted by Grundmann (*Ber.*, 1936, **69**, 1755).

(*c*) To a solution of sodium (100 mg.) in methanol (3 c.c.) was added tropolone methyl ether hemihydrate (50 mg.), and the mixture heated under reflux for 30 minutes. The solution was then evaporated to dryness under reduced pressure and extracted with ether. The residue was acidified, but no benzoic acid could be detected. The ethereal extract was evaporated to small bulk, seeded with tropolone methyl ether, and cooled; filtration gave unchanged tropolone methyl ether (35 mg.). The mother-liquors were evaporated to dryness and the residue heated with a few drops of alcoholic potassium hydroxide; evaporation and acidification again gave no trace of benzoic acid. The presence of methyl benzoate, even in traces, should have been readily detectable by smell.

We are indebted to Dr. E. A. Braude for preliminary ultra-violet absorption measurements and to Dr. J. C. Speakman for the dissociation-constant determination. One of us (A. R. G.) gratefully acknowledges an award from the Department of Scientific and Industrial Research.

THE UNIVERSITY, GLASGOW, W.2. [*Received, October 19th*, 1950.]

108. *The Infra-red Spectrum of Tropolone.*

By H. P. Koch.

The infra-red absorption spectrum of a pure synthetic sample of tropolone has been recorded in the region 3800—650 cm.$^{-1}$ and compared with measurements on certain closely allied synthetic and natural derivatives as well as with relevant data on other related organic structures. Tentative empirical assignments of some of the observed vibration frequencies have been made.

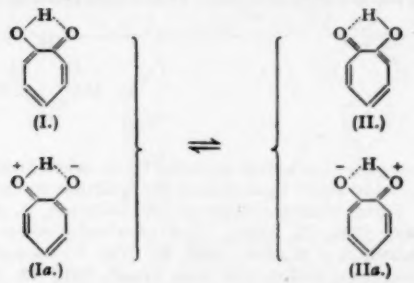
Considerations based on the characteristic OH absorption lead to a tropolone structural model in which the existence of two equivalent energy minima for the location of a highly mobile tautomeric hydrogen is recognised. Infra-red spectrometry may be employed to diagnose the presence or otherwise of the tropolone nucleus in a complex organic structure.

In a complex unsymmetrical molecule such as tropolone (I), nothing like a complete assignment of observed vibration frequencies to specific modes of vibration can be attempted, and no rigorous determination of bond-force constants or molecular geometry can therefore be made. It is well known, however, that the stretching vibration of certain special bonds in a polyatomic molecule may take place almost independently of the rest of the molecule and may very nearly involve the restoring force constant of only that bond. The O–H linkage represents such a special bond *par excellence*, and its nature in a given molecule can therefore be investigated by infra-red absorption technique. From the point of view of tropolone structure, this is fortunate, in that the nature of its hydroxyl bond happens to be a critical feature of the structure as a whole.

The O–H *Region and its Structural Significance.*—In dilute solution in a non-polar solvent, no sharp band near 3600 cm.$^{-1}$ characteristic of similar dilute solutions of simple alcohols or phenols could be observed for tropolone. Instead, there appeared a very broad region of moderate intensity around 3100 cm.$^{-1}$. Similar bands at 3200 cm.$^{-1}$ have been reported by Scott and Tarbell (*J. Amer. Chem. Soc.*, 1950, **72**, 240) for colchiceine and thujaplicin, two naturally occurring derivatives. These results specify rather strong intramolecular association of the hydroxyl group in tropolone, doubtless involving a hydrogen bond with the neighbouring carbonyl-oxygen. The breadth and relatively low intensity of the band are just like those found in a typical β-diketone enol such as acetylacetone (IV), although its frequency position is significantly lower in the latter, at 2700 cm.$^{-1}$ (Rasmussen, Tunnicliff, and Brattain, *ibid.*, 1949, **71**, 1068). This difference indicates appreciably greater strength of internal association in the β-diketones than in tropolones, as would be expected from the sterically much more favourable conditions for hydrogen-bond formation in a six- as against a five-membered ring. It is not possible to calculate the energy (ΔH) of a hydrogen bond from frequency data alone, but spectroscopic comparison with the dimeric carboxylic acids (in which this energy is known from equilibrium studies and gives rise to a broad band around 3000 cm.$^{-1}$) suggests that a figure of ~7 kcals. will be of the right order of magnitude for tropolone. The length of the bond may also be roughly estimated by application of one or other of the approximations relating vibration frequency or force constant to bond length (*e.g.*, Badger, *J. Chem. Physics*, 1934, **2**, 128). It then appears that the frequency shift of the hydroxyl band from its normal "unassociated" position ($-\Delta\nu/\nu$ ~14%) must lead to a lengthening of the normal covalent OH bond distance of 0·98 A. to not more than 1·1 A. in tropolone. Scale models immediately reveal that this estimate precludes anything like a symmetrical equilibrium position of the proton between the two oxygen atoms in the structure. Depending on the precise choice of the other molecular parameters involved (particularly the uncertain CCO and COH angles), we find that the hydroxylic hydrogen is still some 1·5—2·0 A. distant from the carbonyl oxygen with which it is associated. The possibility of electronic resonance degeneracy involving two equivalent bonds between the proton and the two oxygen atoms is therefore ruled out by spectroscopic evidence.

Now, it is known from infra-red data that only *weak* internal hydrogen-bond formation through a five-membered ring arises in the geometrically analogous structures of 2-hydroxy-*cyclo*hexanone (Sheehan, O'Neill, and White, *J. Amer. Chem. Soc.*, 1950, **72**, 3376) or catechol (Wulf and Liddel, *ibid.*, 1935, **57**, 1464). *Strong* hydrogen bonding such as that observed in tropolone can only take place when the donor–acceptor properties of either or both of the

oxygen and hydrogen atoms involved in the bond have been greatly enhanced by some additional structural condition. We are therefore compelled to postulate important resonance contributions from ionic structures such as (I*a*), carrying a formal negative charge on the carbonyl oxygen and a simultaneous increase in the acceptor properties of the proton (cf. Rasmussen *et al.*, *loc. cit.*). Such resonance, of course, implies a "smearing out" of alternate single and double bonds in the presumably planar seven-membered ring. On this geometrical basis, our tropolone model is seen to be related to its tautomeric mirror-image form (II) and (II*a*) by little change other than a "jump" of the proton through some 0·5—1·0 A. A comparable separation of two mirror-image forms has been found to exist in the ammonia molecule (Dennison and Uhlenbeck, *Physical Rev.*, 1932, **39**, 938) and the bifluoride ion (Ketelaar, *Rec. Trav. chim.*, 1941, **60**, 523) where it leads to protonic oscillation between the two equivalent energy minima. Such oscillation is slow compared with the vibration period of the X–H bond and does not confer appreciable additional resonance energy on the structure, but it is extremely rapid from the point of view of tautomeric interconversion. We may, therefore, expect the hydroxylic hydrogen atom of tropolone to be symmetrically located *on a time average basis* between the two oxygen atoms which will thus become chemically indistinguishable, at least in the absence of unsymmetrical nuclear substitution.



The tropolone model resulting from the above discussion based on infra-red absorption data seems to substantiate the modified suggestions made by Dewar (*Nature*, 1945, **155**, 479). Its stabilization energy will correspond approximately to the energy of the hydrogen bond (~7 kcals.) together with the resonance energy of four conjugated double bonds (~17 kcals.; Pauling, *Helv. Chim. Acta*, 1949, **32**, 2241) and the further conjugation of a hydroxyl group (~7 kcals.), totalling about 31 kcals. This stabilization will be diminished by a few kcals. arising from steric strain in the seven-membered ring, and thus accords quite satisfactorily with the experimental thermochemical value of 28·6 kcals. (see preceding paper). Although the apparently close numerical agreement may be fortuitous in view of the many approximations involved, it serves independently to illustrate the energetic plausibility of our structural deductions.

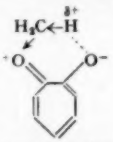
The C–H *Region.*—In the C–H bond stretching vibrations of organic molecules, mechanical coupling often occurs with a resultant splitting of vibrational levels, but the average location of the characteristic absorption near 3000 cm.$^{-1}$ affords some measure of the force constant of such bonds. Unfortunately, this region is partly masked in tropolone by overlapping of the broad OH band and may be further obscured by overtone frequencies of the very intense bands near 1500 cm.$^{-1}$ (see below). The small peaks at 3050 and 3015 cm.$^{-1}$, however, appear to be genuine C–H fundamentals since they could also be observed in the copper derivative of tropolone where OH absorption is, of course, absent and where the 1500 cm.$^{-1}$ region is appreciably different. Their location seems in agreement with that for an unsaturated or aromatic molecule (Fox and Martin, *Proc. Roy. Soc.*, 1940, *A*, **175**, 208), but may be slightly affected by steric strain (see below).

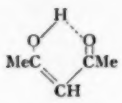
The C=O *Region.*—An impressive mass of evidence has accumulated during the last few years, demonstrating that the carbonyl group in an organic molecule invariably appears to give rise to a characteristic single intense absorption band in the region 1800—1600 cm.$^{-1}$, whatever the other groups attached to the same or adjoining carbon atoms in the molecule and whether or not hydrogen-bond formation occurs (cf. *e.g.*, Hartwell, Richards, and Thompson, *J.*, 1948, 1436; Rasmussen *et al.*, *loc. cit.*, and *ibid.*, p. 1073; Blout, Fields, and Karplus, *J. Amer.*

Chem. Soc., 1948, **70**, 194; Flett, *J.*, 1948, 1441). Moreover, the actual position of the band in this frequency range generally affords a qualitative indication of the force constant or bond order of the carbonyl group involved. Accordingly, Scott and Tarbell (*loc. cit.*) assumed that the first intense infra-red absorption of several naturally occurring tropolones and derivatives near 1620 cm.$^{-1}$ must be associated with the carbonyl group, and they discussed the possible effects of conjugation or hydrogen bonding in connection with the location of the frequency near this lower limit of its normal range.

Tropolone itself exhibits the same intense absorption at 1615 cm.$^{-1}$. Assuming the reasonable but by no means proven premise that the frequency does arise from an approximately independent vibration of the carbonyl bond, we believe that three factors, *viz.*, conjugation, hydrogen bonding, and steric strain, may be jointly responsible for the low force constant involved, but that it is impossible to evaluate the relative importance of these effects on existing evidence. Scott and Tarbell's observation of an unchanged "carbonyl" frequency in a tropolone methyl ether (colchicine) does not necessarily exclude the hydrogen-bonding effect: the structure of *O*-methyltropolones may well involve enhanced stability of the ionic resonance form, promoting internal hydrogen-bond formation between the carbonyl and methyl groups in a sterically favourable six-membered ring (III*a*). Steric strain is expected to lower the carbonyl force constant on the following grounds. In five-membered cyclic carbonyl compounds

(III*a*)





(IV.)

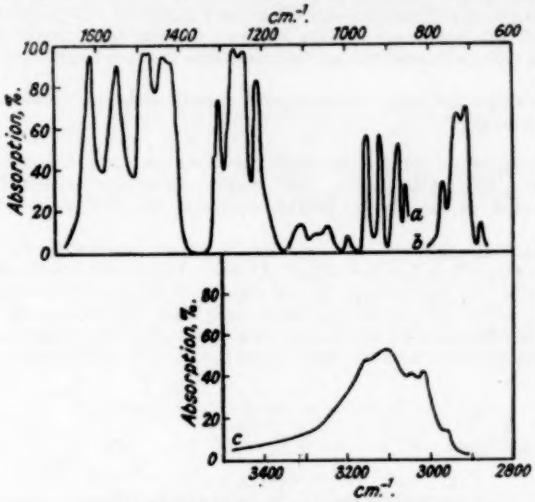
in which ring strain is of opposite sign to that expected in the seven-membered planar tropolone ring, the frequency is invariably *higher* than that of the strainless six-membered ring analogues (Hartwell *et al.*, *loc. cit.*; Jones, Williams, Whalen, and Dobriner, *J. Amer. Chem. Soc.*, 1948, **70**, 2024; Woodward, *ibid.*, 1950, **72**, 3327). This peculiarity seems to be part of a quite general phenomenon (Kohlrausch *et al.*, *Ber.*, 1936, **69**, 729; Coulson and Moffitt, *Phil. Mag.*, 1949, **40**, 1; Plyler and Acquista, *J. Res. Nat. Bur. Stand.*, 1949, **43**, 37; Goubeau, *Annalen*, 1950, **567**, 214) which has a theoretical basis in $s : p$ hybridization ratio changes of the carbon σ valency orbitals (Coulson and Moffitt, *loc. cit.*): all bonds directly attached to a small strained ring become stronger, whereas the bonds forming part of the ring are weakened. In tropolone, the reverse effects should occur since angular strain would here be relieved by an increase rather than decrease of the normal (trigonal) $s : p$ hybridization ratio of the σ valencies in the ring, resulting in a corresponding decrease of the same ratio in the σ orbitals forming the bonds attached to the ring. These changes would lead to a weakening of the carbonyl bond. Insufficient critical data are available to estimate the importance of such an effect in tropolone, but the low vibration frequency (1640 cm.$^{-1}$) of the carbonyl bond in the undoubtedly planar and possibly even more highly strained 4 : 5-benzo*cyclo*hepta-2 : 6-dienone (Scott and Tarbell, *loc. cit.*; Volpin and Plate, *Chem. Abs.*, 1950, **44**, 6846) suggests its real existence in a comparable molecule.

In the crystals or in chloroform solutions of the copper derivative of tropolone, the 1615-cm.$^{-1}$ frequency has been lowered beyond what might be ascribed to a solvent effect to 1590 or 1595 cm.$^{-1}$, respectively. This further decrease may be associated with the secondary co-ordination bond between the carbonyl group and the metal.

The Long-wave Region, 1600—650 *cm.*$^{-1}$.—Beyond the presumed carbonyl frequency at 1615 cm.$^{-1}$, tropolone exhibits an intense band at 1553 cm.$^{-1}$ and other intense and complex absorption at about 1475, 1440, 1255, and 720 cm.$^{-1}$, apart from the smaller and less characteristic bands shown in the figure. Accumulated structure correlation evidence from other organic compounds (*e.g.*, Colthup, *J. Opt. Soc. Amer.*, 1950, **40**, 397) suggests that the 1553-cm.$^{-1}$ band and some at least of the 1500—1400-cm.$^{-1}$ absorption may be associated with in-plane vibrations of the carbon ring, that the 1500—1400-cm.$^{-1}$ region will also contain C–H deformation frequencies, that the complex 1255-cm.$^{-1}$ structure is due to both C–O single bond stretching and O–H deformation vibrations, and that the intense doublet at 720 cm.$^{-1}$ is associated with out-of-plane vibrational modes of the nuclear hydrogen atoms. In the crystalline copper derivative, the 720-cm.$^{-1}$ structure remained almost unchanged, the 1255-cm.$^{-1}$ region was centred at 1230 cm.$^{-1}$, the 1553-cm.$^{-1}$ frequency had apparently been lowered to 1518 cm.$^{-1}$ (1517 cm.$^{-1}$ in chloroform solution), and instead of the broad absorptions in the

1500—1400-cm.$^{-1}$ region there now appeared two narrow bands at 1414 and 1358 cm.$^{-1}$ (in chloroform solution).

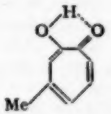
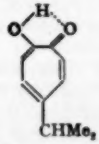
Bands practically identical with the intense tropolone frequencies at 1615, 1553, 1475, 1440, and 1255 cm.$^{-1}$ also occur in β-methyltropolone (V) and γ-thujaplicin (VI) (Scott and Tarbell, *loc. cit.*), and in a carbethoxytropolone which was recently sent to us for infra-red examination (Bartels-Keith and Johnson, *Chem. and Ind.*, 1950, 677). These bands, and particularly those at or near 1615, 1553, and 1255 cm.$^{-1}$, may therefore serve to characterize the



Infra-red spectrum of tropolone.

a, ~9% *in carbon tetrachloride*, 0·1 *mm. path length.*
b, ~3·5% *in carbon disulphide*, 0·1 *mm. path length.*
c, ~2% *in carbon tetrachloride*, 1 *mm. path length.*

presence of the tropolone nucleus in colchicine (Scott and Tarbell, *loc. cit.*) or other complex organic structures. On the other hand, the intense 720 cm.$^{-1}$ doublet of tropolone was not reproduced in the carbethoxy-derivative (Scott and Tarbell did not examine their spectra

(V.)   (VI.)

below 1200 cm.$^{-1}$), just as the analogous absorption region of ethylenic and aromatic derivatives is known to be highly sensitive to changes in nuclear substitution. We may therefore expect that, *e.g.*, α-, β-, and γ-substituted tropolones should be clearly differentiated in this spectral region.

Experimental.—The infra-red spectra of tropolone and its cupric and carbethoxy-derivatives were recorded by standard methods on a Grubb–Parsons single-beam automatic recording spectrometer, employing both sodium chloride and lithium fluoride prisms (cf. Barnard, Fabian, and Koch, *J.*, 1949, 2442). Crystalline specimens were examined as powders in paraffin or perfluorokerosene.

The author is greatly indebted to Prof. J. W. Cook, F.R.S., and Dr. R. A. Raphael for suggesting this investigation and for supplying the necessary material. Thanks are due to Dr. W. E. Moffitt for the benefit of discussion and criticism, and to Miss J. M. Fabian for assistance.

The British Rubber Producers' Research Association,
Welwyn Garden City, Herts.

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109. *Preliminary Syntheses in the Morphine Series. Part II.* The Synthesis of 2-Arylcyclohex-2-enones.*

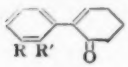
By David Ginsburg and Raphael Pappo.

2-Aryl*cyclo*hex-2-enones are synthesised by three routes, starting from 1-aryl*cyclo*hexenes: (i) allylic bromination with *N*-bromosuccinimide followed by hydrolysis to the carbinol and Oppenauer oxidation; (ii) allylic chlorination with *tert.*-butyl hypochlorite followed by analogous treatment; (iii) formation of the nitrosochloride, conversion into the oxime, and hydrolysis of the latter.

The action of *tert.*-butyl chromate on 1-phenyl*cyclo*hexene yields 3-phenyl-*cyclo*hex-2-enone.

In the intended synthesis of compounds related to morphine, 2-(2 : 3-dimethoxyphenyl)*cyclo*hex-2-enone (I*a*) is a key intermediate. The present communication describes the synthesis of this substance and of the closely related 2-phenyl- (I*b*) and 2-*o*-methoxyphenyl-*cyclo*hex-2-enone (I*c*).

The synthesis of (I*a*) from the corresponding difficultly accessible saturated ketone (II) (Part I;* cf. Horning, Horning, and Platt, *J. Amer. Chem. Soc.*, 1947, **69**, 2929) was not fruitful. Bromination of this ketone in the 2-position, followed by dehydrobromination, gave poor results. (After this study had been completed, Bachmann and Wick, *J. Amer. Chem. Soc.*, 1950, **72**, 339, reported satisfactory results with this method in the case of 2-phenyl-*cyclo*hexanone.) Alternative methods were investigated, all using 1-aryl*cyclo*hexenes (III) as starting materials.



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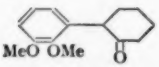
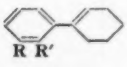
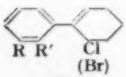


(II.)



(III.)



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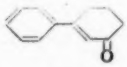

(V.)

(*a*) R = R′ = OMe; (*b*) R = R′ = H; (*c*) R = H, R′ = OMe.

(*a*) Allylic bromination of 1-aryl*cyclo*hexenes (III) with *N*-bromosuccinimide yielded apparently only one of the possible brominated allylic compounds. Hydrolysis to the carbinol, followed by Oppenauer oxidation, yielded compounds of structure (I). The hydrolysis of the allylic halides (IV) may well involve allylic rearrangement (Young and Andrews, *ibid.*, 1944, **66**, 420) but inspection of formula (IV) will show that both direct hydrolysis, and rearrangement plus hydrolysis, will result in the same carbinol.

(*b*) Chlorination of type (III) compounds with *tert.*-butyl hypochlorite gave, presumably through addition of the reagent to the double bond and subsequent loss of *tert.*-butanol, the chlorinated allylic products (cf. Ritter and Ginsburg, *ibid.*, 1950, **72**, 2381; see, however, Teeter and Jackson, *J. Amer. Oil Chem. Soc.*, 1949, **26**, 535). As in method (*a*), the chloro-compounds were converted into the corresponding ketones (I).

(*c*) Treatment of compounds (III) with nitrosyl chloride (formed *in situ*) gave nitroso-chlorides which were converted into the oximes, and these were hydrolysed to the αβ-unsaturated ketones (I).

Methods (*a*) and (*b*) were less suited than (*c*) to the synthesis of compounds of type (I), because of the difficulty attending the production of αβ-unsaturated alcohols from allylic halides (Young and Andrews, *loc. cit.*; Catchpole, Hughes, and Ingold, *J.*, 1948, 8), the formation of a hydrocarbon in addition to the alcohol, and the tediousness of the Oppenauer method of oxidation. Method (*c*) had none of these drawbacks and, in the case of the ketone (I*a*) which was the most important for further work, overall yields of 40—50% were obtained from 1-(2 : 3-dimethoxyphenyl)*cyclo*hexene (III*a*) *via* the nitrosochloride and the oxime.

An attempt was made to obtain ketones of type (I) directly from the unsaturated hydrocarbons (III) by means of *tert.*-butyl chromate (Oppenauer and Oberrauch, *Anal. Asoc. Quím. Argentina*, 1949, **37**, 246). Oxidation took place exclusively in the alternative allylic position, and 3-phenyl*cyclo*hex-2-enone (V) was obtained in 22% yield. This reagent acts, therefore,

* The paper entitled "A Synthesis of 2-(2 : 3-Dimethoxyphenyl)*cyclo*hexanone" (*J.*, 1950, 1369) is regarded as Part I of this series.

on 1-phenyl*cyclo*hexene similarly to chromic acid, which in the hands of Fieser and Szmuszkovicz (*J. Amer. Chem. Soc.*, 1948, **70**, 3352) gave small amounts of (V).

Experimental.

(M. p.s and b. p.s are uncorrected.)

1-o-*Methoxyphenyl*cyclo*hexene* (III*c*).—To the Grignard reagent, prepared from *o*-bromoanisole (486 g., 2·6 moles) and magnesium (63·1 g., 2·6 atoms) in ether (2·5 l.), under reflux (1 hour), was added *cyclo*hexanone (255 g., 2·6 moles) in ether (250 ml.), with stirring, at 0—5°. A viscous mass formed, making further stirring difficult. The mixture was refluxed for 3 hours, kept overnight, and decomposed with saturated ammonium chloride solution. The ethereal layer was washed with water and dried and the product distilled at 0·05 mm. pressure. 1-o-*Methoxyphenyl*cyclo*hexanol* (398 g., 75%) crystallised spontaneously and melted at 54—55° (from light petroleum) (Found: C, 75·6; H, 8·7. $C_{13}H_{18}O_2$ requires C, 75·7; H, 8·7%).

The tertiary carbinol was dehydrated by azeotropic distillation with anhydrous oxalic acid and toluene (Part I, *loc. cit.*), in quantitative yield. 1-o-*Methoxyphenyl*cyclo*hexene* boiled at 105—110°/0·8 mm. It melted at 17·1° (Found: C, 83·6; H, 8·8. $C_{13}H_{16}O$ requires C, 83·0; H, 8·5%).

In the same manner, 1-*phenyl*cyclo*hexene* (III*b*) was prepared (cf. von Auwers and Treppmann, *Ber.*, 1915, **48**, 1216), b. p. 132—135°/17 mm., m. p. 0°. 1-(2 : 3-Dimethoxyphenyl)*cyclo*hexanol was prepared as in Part I. The time required for the metalation of veratrole with butyl-lithium, according to Gilman, Swiss, and Cheney (*J. Amer. Chem. Soc.*, 1940, **62**, 1965), could be reduced from 24 to 3 hours without materially affecting the yield.

Preparation of 2-*Aryl*cyclo*hex*-2-*enols.*—(A) *Bromination with N-bromosuccinimide.* 1-Phenyl*cyclo*hexene (III*b*) (20 g.) and *N*-bromosuccinimide (22 g.) were refluxed in carbon tetrachloride (100 ml.) for 1 hour (a little hydrogen bromide was evolved). The succinimide was removed and the filtrate concentrated *in vacuo*. The residual oil was heated with potassium acetate (20 g.) in 75% acetic acid (500 ml.) for 8 hours at 60°. Most of the solvent was removed *in vacuo*, and the residue taken up in ether. After being washed with sodium carbonate solution, the ether was distilled off, and the residual oil dissolved in 10% methanolic potassium hydroxide (100 ml.) and boiled for one hour. Concentration *in vacuo*, addition of water, extraction with ether, and fractionation in a high vacuum yielded two fractions (and some polymeric material): (i) B. p. 80—110°/0·05 mm. (4 g.), chiefly *phenyl*cyclo*hexadiene* (contaminated with some starting material), which crystallised and melted at 55—58° (from light petroleum) (Found: C, 92·5; H, 7·7. $C_{12}H_{12}$ requires C, 92·3; H, 7·7%). Berlande (*Bull. Soc. chim.*, 1942, **9**, 642) has reported m. p. 66° for 1-phenyl*cyclo*hexa-1 : 3-diene. (ii) B. p. 110—125°/0·05 mm., 2-phenyl*cyclo*hex-2-enol (11 g., 50%), the *phenylurethane* of which melted at 152—153° (from methyl*cyclo*hexane) (Found: N, 4·7. $C_{19}H_{19}O_2N$ requires N, 4·8%).

(B) *Chlorination with* tert.*-butyl hypochlorite.* To 1-phenyl*cyclo*hexene (III*b*) (111 g., 0·7 mole) in boiling carbon tetrachloride (225 ml.), *tert.*-butyl hypochlorite (80 g.) was added during 30 minutes. Heating was continued for 1 hour and the solvent and *tert.*-butanol were removed *in vacuo*. The crude residue (110 g.) was heated under reflux for 8 hours with potassium acetate (73 g.), acetic acid (550 ml.), and water (180 ml.). Further treatment as described under (A) yielded fractions, (i) b. p. 90—110°/0·05 mm. (25 g.), (ii) b. p. 110—130°/0·05 mm., 2-phenyl*cyclo*hex-2-enol (51 g.), and (iii) polymeric material.

1-o-Methoxyphenyl*cyclo*hexene (III*c*) (132 g., 0·7 mole) with *tert.*-butyl hypochlorite (80 g.) in carbon tetrachloride (265 ml.) similarly yielded fractions, (i) b. p. 80—90°/0·05 mm. (21 g.), consisting largely of mono- and di-olefin, (ii) b. p. 90—115°/0·05 mm., 2-*o*-methoxyphenyl*cyclo*hex-2-enol (48 g.), and (iii) polymeric material. The *phenylurethane* from (ii) melted at 135° (crystallised from methyl*cyclo*hexane) (Found: N, 4·3. $C_{20}H_{21}O_3N$ requires N, 4·3%).

Treatment of the allylic chloro-compounds with silver nitrate did not increase the yields of $\alpha\beta$-unsaturated alcohols.

Preparation of 2-*Aryl*cyclo*hex*-2-*enones.*—A. *Oppenauer oxidation of* 2-*aryl*cyclo*hex*-2-*enols.* A mixture of 2-phenyl*cyclo*hex-2-enol (17·8 g.), aluminium *tert.*-butoxide (40 g.), acetone (400 ml.), and dry benzene (1600 ml.) was heated under reflux for 17 hours, and worked up in the usual manner. After removal of mesityl oxide (a by-product) *in vacuo*, the product solidified. It consisted of unchanged 2-phenyl*cyclo*hex-2-enol (4 g.; identified as the phenylurethane) and 2-phenyl*cyclo*hex-2-enone (I*b*), m. p. 96—97° (11 g.) (Found: C, 83·7; H, 7·3. Calc. for $C_{12}H_{12}O$: C, 83·6; H, 7·0%). Bachmann and Wick (*loc. cit.*) report m. p. 95—95·5°. The *oxime* melted at 151° (from ethanol) (Found: C, 76·7; H, 7·0; N, 7·8. $C_{12}H_{13}ON$ requires C, 77·0; H, 6·95; N, 7·5%). The 2 : 4-*dinitrophenylhydrazone* formed orange-red crystals (from chloroform–ethanol), m. p. 165—166°, $\lambda_{max.}$ 3800 A., $\varepsilon_{max.}$ = 25,800 (in anhydrous ethanol) (Found: C, 61·5; H, 4·5; N, 16·2. $C_{18}H_{16}O_4N_4$ requires C, 61·4; H, 4·5; N, 15·9%).

2-*o*-Methoxyphenyl*cyclo*hex-2-enol was oxidised similarly. The resulting 2-*o*-methoxyphenyl-*cyclo*hex-2-enone (I*c*) crystallised from the reaction mixture (40% yield) only after seeding, and after recrystallisation from hexane, melted at 53°.

Proof of structure of 2-*aryl*cyclo*hex*-2-*enones* (I). (i) *Dehydrogenation.* 2-Phenyl*cyclo*hex-2-enone (I*b*) (1 g.) in *p*-cymene (10 ml.) was heated under reflux for 2 hours with 5% palladium–charcoal (2 g.) in a current of carbon dioxide. The catalyst was removed by filtration and washed with benzene, the filtrate extracted with 10% aqueous sodium hydroxide, and the extract saturated with carbon dioxide. A pinkish-white precipitate (0·8 g.) was obtained which, recrystallised from light petroleum, had m. p. 57° alone or on admixture with authentic 2-hydroxydiphenyl (Hückel *et al.*, *Annalen*, 1930, **477**, 123, report m. p. 58°). For such hydrogenations compare Horning, Horning, and Walker, *J. Amer. Chem. Soc.*, 1949, **71**, 169; Horning and Horning, *ibid.*, 1947, **69**, 1359.

(ii) *Reduction.* 2-(2 : 3-Dimethoxyphenyl)*cyclo*hex-2-enone (I*a*) (1 g.) in 95% ethanol (11 ml.) was hydrogenated in presence of 5% palladium–charcoal (0·5 g.), at room temperature and 60 lbs./sq. in pressure. One mole of hydrogen was taken up. The catalyst was removed by filtration and the solvent evaporated. Recrystallisation of the solid residue from light petroleum gave pure 2-(2 : 3-dimethoxyphenyl)*cyclo*hexanone (II), m. p. 71° alone or on admixture with an authentic sample (Part I, *loc. cit.*).

(iii) The ultra-violet absorptions of the 2 : 4-dinitrophenylhydrazones agree with those reported by Braude and Jones (*J.*, 1945, 497) for derivatives of $\alpha\beta$-unsaturated ketones.

Further proof of the position of the double bond will be offered in a subsequent communication.

B. *Through nitrosochlorides of* 1-*aryl*cyclo*hexenes* (III). *Formation of nitrosochlorides.* The example given refers to 1-(2 : 3-dimethoxyphenyl)*cyclo*hexene (III*a*) but the procedure is general. To a mixture of the *cyclo*hexene (0·1 mole, 21·3 g.), amyl nitrite (0·12 mole, 13·8 g.), and acetic acid (25 ml.), 30% hydrochloric acid (12 ml.) was added dropwise with stirring. The temperature during the addition, which required 30 minutes, was kept at −10°, and the mixture stirred for a further 3 hours at −10°. The colour, initially brown, soon became green. The white microcrystalline nitrosochloride was filtered off with suction and washed thoroughly with ice-cold ethanol. The yields were 60—70% of 1-phenyl*cyclo*hexene nitrosochloride, m. p. 110° (decomp.), 1-*o*-methoxyphenyl*cyclo*hexene nitrosochloride, m. p. 106° (decomp.), and 1-(2 : 3-dimethoxyphenyl)*cyclo*hexene nitrosochloride, m. p. 125° (decomp.). The nitrosochlorides are insoluble in most organic solvents. They are soluble in chloroform, but decompose in solution. They also decompose on storage. For this reason, they were not recrystallised, but were used immediately for the next step.

Conversion of the nitrosochlorides into 2-*aryl*cyclo*hex-2-enone oximes.* The dry nitrosochloride (0·1 mole) was suspended in pyridine (30 ml.), and the mixture heated to 60—70°, an exothermic reaction then setting in, which often caused boiling and dissolution.

In the case of 1-phenyl*cyclo*hexene nitrosochloride, a slight excess of 20% aqueous potassium hydroxide (0·11 mole) was added and the mixture swirled for a few minutes. Sufficient acetic acid was added to neutralise the pyridine and potassium hydroxide present, and then water (200 ml.) 2-Phenyl*cyclo*hex-2-enone oxime crystallised from the mixture. It was filtered off, washed with water, and recrystallised from ethanol, and had m. p. 151° (yield, 70—80%). It was identical with the oxime prepared by the other methods described above.

In the case of 1-(2 : 3-dimethoxyphenyl)*cyclo*hexene nitrosochloride, the reaction mixture was diluted with ether, and the ethereal solution washed with a small volume of 10% aqueous potassium hydroxide and extracted with excess of Claisen alkali solution. The alkaline layer was diluted five-fold with water and acidified with acetic acid. 2-(2 : 3-*Dimethoxyphenyl*)cyclo*hex-2-enone oxime* was precipitated; recrystallised from ethanol, it had m. p. 130° (Found : C, 67·9; H, 6·9; N, 5·7. $C_{14}H_{17}O_3N$ requires C, 68·0; H, 6·9; N, 5·7%). 1-*o*-Methoxyphenyl*cyclo*hexene nitrosochloride, treated analogously, gave 2-*o*-*methoxyphenyl*cyclo*hex-2-enone oxime*, m. p. 150° (Found : C, 71·7; H, 6·8; N, 6·6. $C_{13}H_{15}O_2N$ requires C, 71·9; H, 6·9; N, 6·4%).

The yields varied from 70 to 80%.

Conversion of the oximes into the ketones (I). The oxime (0·5 mole), concentrated sulphuric acid (200 g.), and water (2 l.) were refluxed for 1 hour. The mixture was cooled, and the $\alpha\beta$-unsaturated ketone filtered off, washed with water until neutral, dried, and distilled in a high vacuum. Thus were obtained 2-phenyl*cyclo*hex-2-enone (I*b*), m. p. 96° (from methyl*cyclo*hexane), identical with the product described above, 2-*o*-*methoxyphenyl*cyclo*hex-2-enone* (I*c*), m. p. 53° (Found : C, 77·5; H, 7·1. $C_{13}H_{14}O_2$ requires C, 77·2; H, 6·9%) [2 : 4-*dinitrophenylhydrazone*, orange, m. p. 179—180°, $\lambda_{max.}$ 3820 A., $\varepsilon_{max.}$ = 24,400 (in anhydrous ethanol) (Found : C, 59·8; H, 4·8; N, 14·7. $C_{19}H_{16}O_5N_4$ requires C, 59·7; H, 4·7; N, 14·7%)]; and 2-(2 : 3-*dimethoxyphenyl*)cyclo*hex-2-enone* (I*a*), m. p. 96° (from butanol) (Found : C, 72·4; H, 6·9. $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·9%) [2 : 4-*dinitrophenylphenylhydrazone*, red, m. p. 141° (from ethanol), $\lambda_{max.}$ 3810 A., $\varepsilon_{max.}$ = 25,200 (in anhydrous ethanol) (Found : C, 57·7; H, 4·65; N, 13·9. $C_{20}H_{20}O_6N_4$ requires C, 58·3; H, 4·9; N, 13·6%); *semicarbazone*, m. p. 190·5—191·5° (from ethanol) (Found : C, 62·5; H, 6·5; N, 14·5. $C_{15}H_{19}O_3N_3$ requires C, 62·3; H, 6·6; N, 14·5%)].

The yields from the crude oximes were 90—95%, and the overall yields from the 1-aryl*cyclo*hexenes (without purification of intermediates) were 40—50%.

Oxidation of 1-*Phenyl*cyclo*hexene* (III*b*) *with* tert.-*Butyl Chromate* (Oppenauer and Oberrauch, *loc. cit.*).—Chromic anhydride (0·8 mole, 80 g.) was added with stirring during 10 minutes to *tert.*-butanol (200 ml.) with external cooling (to <20°). To the dark-red solution was added carbon tetrachloride (680 ml.), and vigorous stirring was continued for 10 minutes after addition of anhydrous sodium sulphate. The solution was filtered, the solid washed with a small volume of carbon tetrachloride, and the filtrate concentrated *in vacuo* (water pump; internal temp. <30°) to a volume of 200 ml. (solution *A*).

To a solution of 1-phenyl*cyclo*hexene (III*b*) (20 g.) in carbon tetrachloride (560 ml.), were added glacial acetic acid (80 ml.), acetic anhydride (4 ml.), and solution *A* (200 ml.). During the first hour the temperature was allowed to rise to 40°. Then the mixture was kept at room temperature for 4 days and added in portions with stirring and cooling to a suspension of oxalic acid (200 g.) in water (1 l.) in a large vessel (foaming !). Stirring was continued for 3 hours. The upper aqueous layer was extracted with carbon tetrachloride (200 ml.), and the combined organic extracts were washed with two portions of 10% potassium hydroxide solution. The carbon tetrachloride was removed by distillation at atmospheric pressure and the residue distilled *in vacuo*. The distillate (17 g.) partly crystallised on cooling, and consisted of 3-phenyl*cyclo*hex-2-enone (V) and some unchanged 1-phenyl*cyclo*hexene. Recrystallisation from hexane yielded pure 3-phenyl*cyclo*hex-2-enone (5 g.), m. p. 64° (Abdullah, *J. Indian Chem. Soc.*, 1935, **12**, 62, reports m. p. 64°; Downes, Gill, and Lions, *J. Amer. Chem. Soc.*, 1950, **72**,

3464, report m. p. 64·5°). The ketone is quite soluble in 1-phenyl*cyclo*hexene. No attempt was made to improve the yield.

The 2 : 4-dinitrophenylhydrazone melted at 220—221° (Downes, Gill, and Lions, *loc. cit.*, report m. p. 221°), and had $\lambda_{max.}$ 3950 A., $\varepsilon_{max.}$ = 51,000 (in anhydrous ethanol).

The ultra-violet absorption data reported in this paper were determined by Dr. Y. Hirshberg of this Institute. This paper represents part of a thesis submitted by Raphael Pappo to the Hebrew University, Jerusalem, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

DANIEL SIEFF RESEARCH INSTITUTE, WEIZMANN INSTITUTE OF SCIENCE,
REHOVOTH, ISRAEL. [*Received, October 30th*, 1950.]

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110. *Interaction of Alcohols with Silicon Tetrachloride.*

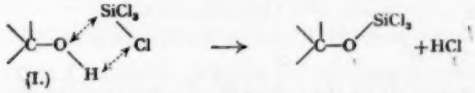
By W. GERRARD and A. H. WOODHEAD.

(+)-Octan-2-ol and silicon tetrachloride formed chlorosilanes and tetra-2-octyloxysilane in proportions depending on the proportion of silicon tetrachloride, but none of the chloride, RCl. (+)-1-Phenylethanol formed considerably racemised chloride, RCl, under similar conditions. Whereas hydrogen chloride had no action on tetra-2-octyloxysilane, it rapidly dealkylated the corresponding (+)-1-phenylethyl compound, the chloride formed being considerably racemised. In the presence of pyridine a number of tetra-alkyloxysilanes have been obtained in excellent yield. These and other data are now available for comparison with those from a study of phosphorus trichloride–alcohol systems, and provide a contribution to the eventual elucidation of mechanism.

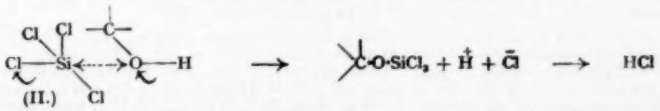
THE chlorosilanes $RO{\cdot}SiCl_3$, $(RO)_2SiCl_2$, $(RO)_3SiCl$, and the tetra-alkyloxysilane $(RO)_4Si$, were obtained from silicon tetrachloride and (+)-octan-2-ol in proportions depending on the relative amounts of the reagents, whereas formation of 2-chloro-octane was not observed. On the other hand, (+)-1-phenylethanol and the tetrachloride afforded hydrated silica and almost completely racemised 1-chloro-1-phenylethane in large yield.

Tertiary alcohols such as *tert.*-butyl alcohol and 2-methylbutan-2-ol behaved similarly to 1-phenylethanol, except that when mixed with silicon tetrachloride they showed a remarkable reluctance to react. When the mixture was warmed a reaction became vigorous, and hydrated silica (91% yield) was rapidly formed, the other product isolated being the corresponding chloride, RCl.

Formation of the silicon esters may be depicted as due to four-centre, broadside approach of the molecules as in (I), there being but one transition state.



We prefer this picture to an end-on three-centre process shown in (II).



Addition of silicon tetrachloride to a pentane solution of pyridine and the appropriate alcohol readily afforded pyridine hydrochloride and the tetra-alkyloxysilane in excellent yield, thus demonstrating facilitation of broadside approach (I), presumably by hydrogen bond-formation, $ROH{\cdot}{\cdot}{\cdot}NC_5H_5$ (Gerrard, *J.*, 1939, 99). In this system 1-phenylethanol behaved similarly. In the examples of the two tertiary alcohols mentioned, replacement of the third and the fourth chlorine atom could not be effected at room temperature, although the third was replaced when the system was heated. Miner, Bryan, Holysz, and Pedlow (*Ind. Eng. Chem.*, 1947, **39**, 1368) introduced the use of pyridine to effect the formation of dichlorodi-(2-methyl-2-butyloxy)silane and dichlorodi-(*tert.*-butyloxy)silane for the immediate purpose of replacing the chlorine atoms by amino-groups. We extended observations to emphasise the existence of a pronounced

example of what we believe to be steric hindrance to the broadside approach of a third molecule of a tertiary alcohol in the stepwise replacement of chlorine by alkoxyl, in the presence of pyridine, although ethanol is well able to continue the precipitation of pyridine hydrochloride. Models show possible hindrance to the approach of a third tertiary alcohol molecule by the four-centre, broadside mechanism (I), although certain other modes of approach are not so restricted. A very similar effect was noticed by Gerrard and Wyvill (*Research*, 1949, **2**, 536) with respect to trichloro-*tert.*-butyl alcohol and phosphorus trichloride. There was no evidence of hindrance in the example of 1:3-dimethylbutyl alcohol (see table, p. 521) in the silicon tetrachloride system, thus showing the inadequacy in this respect of a slightly more remote branching.

Hydrogen chloride readily effected dealkylation of (+)-tetra-(1-phenylethoxy)silane at −10°, hydrated silica being precipitated, and much-racemised (−)-1-chloro-1-phenylethane being formed in 94% yield. Under similar conditions, (+)-tetra-(2-octyloxy)silane was unaffected by hydrogen chloride.

So far as 1-phenylethanol is concerned, the alcohol–silicon tetrachloride system bears strong analogy with the alcohol–phosphorus trichloride system (Gerrard, *J.*, 1944, 85), presumably because the directing feature is the activity of the alcoholic carbon atom. In the example of octan-2-ol, the systems differ, because the lone pair of electrons on the phosphorus atom of the phosphite $(RO)_3P$ facilitates removal of *one* alkyl group by hydrogen chloride thus : $(RO)_3P + HCl \longrightarrow (RO)_2P(=O)H + RCl$. The lone pair not being available in the silicon series, it is not surprising that dealkylation is very slow.

Tetra-esters containing branched alkyl groups showed a reluctance to disproportionation with silicon tetrachloride attributed to the screening effect of the branches which form a network round the tetrahedron of which the silicon atom is the centre.

The (+)-2-octyloxychlorosilanes have been described by Gerrard and Woodhead (*Research*, 1949, **2**, 48).

Experimental.

It is stated when reaction mixtures were washed with water, and an aqueous solution of sodium carbonate was also employed, the organic liquids being dried with potassium carbonate and sodium sulphate. Pyridine hydrochloride was separated and analysed without further purification (Calc. : Cl, 30·7; C_5H_5N, 68·4%).

Rotatory powers are stated for $l = 1$, and are expressed always in terms of the (+)-alcohols, although (−)-alcohols were also employed.

Interaction of Silicon Tetrachloride and Alcohols in the Presence of Pyridine.—Silicon tetrachloride (8·5 g., 0·25 mol.) in pentane (10 c.c.) was added dropwise to a solution of (+)-octan-2-ol (26 g., 1 mol.; a_D^{18} +7·28°) and pyridine (15·8 g., 1 mol.) in pentane (125 c.c.) at −10°. Pyridine hydrochloride (Found : Cl, 30·6; C_5H_5N, 68·2%) was quantitatively precipitated, and from the pentane solution (+)-tetra-2-octyloxysilane, b. p. 190°/0·3 mm., a_D^{18} +16·32° (see table), was obtained.

The silane (5 g.) was heated under reflux for 8 hours with an alcoholic solution of potassium hydroxide (10%). The liquid was then diluted with water and, from the washed and dried pentane extract, (+)-octan-2-ol (4·0 g.), b. p. 81°/18 mm., a_D^{20} +7·32°, was obtained.

Dry hydrogen chloride was passed for 2 hours into a pentane solution of (+)-tetra-2-octyloxysilane at −10°. No reaction occurred.

Passage of dry hydrogen bromide into (+)-tetra-2-octyloxysilane [8 g.; a_D^{18} +17·08°; from (+)-alcohol, a_D^{18} +7·76°] in pentane (15 c.c.) for 3 hours at −10° gave small amounts of silica and a mixture (0·5 g.) of alcohol and bromide, b. p. 80°/15 mm., a_D^{18} +4·6° (Found : Br, 11·3%); the tetra-ester (5·1 g.), b. p. 185°/0·5 mm., containing probably a little bromosilane, $(RO)_3SiBr$ (Found : Br, 4·6%), was in the main recovered. There was a residue (2·0 g.) which gelled on being cooled.

Passage of hydrogen iodide through (+)-tetra-2-octyloxysilane (5·44 g.; a_D^{18} +17·08°) for 2 hours at −10° caused the precipitation of hydrated silica (0·75 g. Calc. as SiO_2,H_2O, 0·78 g.) (Found : SiO_2, 77·4. Calc. for SiO_2,H_2O : SiO_2, 76·9%). From the washed and dried pentane filtrate, a mixture of alcohol and iodide (2·5 g.), b. p. 84—90°/17 mm., a_D^{18} −27·36° (Found : I, 30·7%), and the iodide (3·5 g.), b. p. 90—94°/17 mm., a_D^{18} −35·4° (Found : I, 51·4. Calc. for $C_8H_{17}I$: I, 52·9%), were obtained. Some loss of material is attributable to adsorption on the silica, the leaching solvents not being incorporated with the primary pentane filtrate.

Silicon tetrachloride (8·5 g., 0·25 mol.) in *n*-pentane (10 c.c.) was added dropwise to a pentane (50 c.c.) solution of (+)-1-phenylethanol (24·4 g., 1 mol.; a_D^{18} +24·0°) and pyridine (15·8 g., 1 mol.) at −10°, with vigorous stirring. Precipitation of pyridine hydrochloride occurred immediately, and after 1 hour it (20·9 g.) (Found : Cl, 30·7. C_5H_5N, 68·1%) was separated by filtration.

From the filtrate, (+)-alcohol (2·0 g.), b. p. 95°/12 mm., a_D^{18} +22·12°, and (+)-*tetra*-1-*phenylethoxysilane* (20 g.) (see table), b. p. 220°/0·2 mm., a_D^{18} +59·0°, were obtained. Formation of chloride was not detected.

This silane (5 g.) was heated with alcoholic potassium hydroxide as described for the 2-octyl analogue, but hydrolysis was much slower, 24 hours being required. The (+)-alcohol (96%), b. p. 93°/12 mm., a_D^{20} +23·6°, was obtained.

The silane (5 g.), when heated under reflux for 12 hours with an alcoholic solution of hydrochloric acid (5% of concentrated acid in alcohol), afforded (−)-1-chloro-1-phenylethane (4·0 g.), b. p. 80°/25—20 mm., α_D^{18} −2·32° (Found : Cl, 25·1. Calc. : Cl, 25·3%).

(+)-Tetra-1-phenylethoxysilane (5·12 g.; α_D^{18} +57·2°) in pentane (25 c.c.) afforded a steady precipitation of hydrated silica (0·74 g. Calc. : 0·78 g.) and (−)-1-chloro-1-phenylethane (4·5 g.), b. p. 80°/25 mm., α_D^{18} −3·92° (Found : Cl, 24·9. Calc. for C_8H_9Cl : Cl, 25·3%), whilst hydrogen chloride was passed through the mixture for 3 hours at −10°. The loss of material by adsorption on the silica (see previous statement) being considered, the yield of chloride, based on the weight of hydrated silica, was about 94%.

Passage of hydrogen bromide into (+)-tetra-1-phenylethyloxysilane (8·0 g.; α_D^{18} +59·0°; from alcohol, α_D^{18} +24·0°) at −10° afforded (−)-1-bromo-1-phenylethane (8·5 g.), b. p. 88°/14 mm., α_D^{18} −1·0° (Found : Br, 43·4. Calc. for C_8H_9Br : Br, 43·2%), and hydrated silica (0·95 g.).

(+)-Tetra-1-phenylethoxysilane (5·12 g.; α_D^{18} +59·0°) and hydrogen iodide afforded hydrated silica (0·75 g. Calc. : 0·78 g.) and what appeared to be the iodide, α_D^{18} 0° but, immediately after each washing and drying, iodine was liberated, and distillation was not successfully performed.

In the table are recorded results obtained when silicon tetrachloride (8·5 g., 0·25 mol.), the appropriate alcohol (1 mol.), and pyridine (15·8 g., 1 mol.) were mixed in pentane solution (50 c.c.) at −10°. The calculated amount of pyridine hydrochloride is 23·1 g.

Alcohol.	B. p./0·5 mm.	$(RO)_4Si$, yield, %.	Found, %. C.	Found, %. H.	Calc., %. C.	Calc., %. H.	C_5H_5N,HCl, g.
n-Butyl	106—108°	88	60·0	11·05	60·0	11·25	22·5
sec.-Butyl	86—88	94	60·0	11·23	60·0	11·25	22·3
*iso*Butyl	90—91	92	59·7	11·2	60·0	11·25	22·5
1-Octyl	205—210	96	70·7	12·5	70·6	12·5	22·8
2-Octyl	193	85	70·8	12·5	70·6	12·5	23·0
1 : 3-Dimethylbutyl	122	92	67·3	12·2	66·6	12·0	22·6
1-Carbethoxyethyl	178—179	92	48·6	7·1	48·4	7·25	22·8
1-Phenylethyl	220	77	74·8	7·2	75·0	7·1	20·9

Silicon tetrachloride (8·5 g., 0·25 mol.) in *n*-pentane (10 c.c.), added dropwise to a solution of 2-methylbutan-2-ol (17·6 g., 1 mol.) and pyridine (15·8 g., 1 mol.) in *n*-pentane (40 c.c.) at −10°, caused immediate precipitation of pyridine hydrochloride, but the amount (12·6 g.) (Found : Cl, 30·55. C_5H_5N, 68·2%), even after the mixture had been set aside at 15° for 12 hours, was only a half of that expected (23·1 g.). The filtered solution was distilled, and a mixture of pyridine and alcohol (14 g.), b. p. 100—118°, was first obtained, followed by dichlorodi-(2-methyl-2-butoxy)silane (10·5 g.), b. p. 112—115°/25 mm. (Found : Cl, 26·2; Si, 10·1. Calc. for $C_{10}H_{22}O_4Cl_2Si$: Cl, 26·0; Si, 10·25%). Miner, Bryan, Holysz, and Pedlow (*loc. cit.*) obtained their compound from reactants in the molecular ratios $SiCl_4$: ROH : C_5H_5N = 0·5 : 1 : 1, thereby effecting a complete removal of alcohol and pyridine. Our purpose was to give the reagents every opportunity to form the tetra-ester. We repeated the experiment with the proportions used by these workers and obtained pyridine hydrochloride (11·25 g. Calc. : 11·55 g.) and the chlorosilane, b. p. 112—115°/25 mm. (Found : Cl, 26·1%). The mixture obtained from silicon tetrachloride (4·25 g., 0·25 mol.), pyridine (7·9 g., 1 mol.), and the alcohol (20 g., 2·3 mols. excess) was heated under reflux for 4 hours in absence of solvent. Pentane was added and the precipitate (10·4 g.) (Found : Cl, 28·7; SiO_2, 4·1; C_5H_5N, 64·5%) was not pure hydrochloride. From the filtered solution, unchanged alcohol and pyridine, b. p. 100—117°, and chlorotri-(2-methyl-2-butoxy)silane (4·5 g.) b. p. 87—89°/0·5 mm. (Found : Cl, 11·1; Si, 8·4. Calc. : Cl, 10·94; Si, 8·6%), were obtained. There was a considerable amount of solid siliceous residue. Miner *et al.* (*loc. cit.*) obtained this chlorosilane by using pyridine and alcohol in proportions equivalent to three of the four atoms of chlorine in the tetrachloride. Our purpose was to eliminate the fourth atom as well.

It has been shown above that at room temperature only half the chlorine in silicon tetrachloride (0·25 mol.) is precipitated as pyridine hydrochloride in the interaction with the alcohol (1 mol.) in the presence of pyridine (1 mol.). When ethanol (0·5 mol.) was added to this mixture the remainder of the chlorine was readily precipitated as the hydrochloride (total weight, 11·3 g. Calc. : 11·55 g.).

Analogous results were obtained with *tert.*-butyl alcohol. This (1 mol.) with silicon tetrachloride (0·25 mol.) in the presence of pyridine (1 mol.) in pentane solution precipitated as pyridine hydrochloride only half of the chlorine present. Dichlorodi-*tert.*-butoxysilane can be obtained in good yield by the distillation of the filtered solution, b. p. 74°/18 mm. (cf. Miner *et al.*, who obtained this chlorosilane, b. p. 70°/15 mm., by using 0·5 mol. of tetrachloride for each mol. of alcohol and of pyridine). If, however, butan-2-ol (0·5 mol.) or 1-phenylethanol (0·5 mol.) is added to the undistilled mixture, precipitation of pyridine hydrochloride continues (21·3 g. Calc. : 23·1 g.) and accounts for nearly all the chlorine present.

Interaction of Silicon Tetrachloride and Alcohols in Absence of Pyridine.—(+)-Octan-2-ol (13·0 g., 1 mol.; α_D^{18} +8·0°) in *n*-pentane (20 c.c.) was added dropwise (1 hour) to a pentane (25 c.c.) solution of silicon tetrachloride (17 g., 1 mol.) at 0°. After an hour volatile matter was removed in a vacuum at 15°, and from the residue (+)-trichloro-2-octyloxysilane (15·5 g.), b. p. 100°/16 mm., α_D^{18} +14·0° (Found : Cl, 41·0; Si, 10·3. Calc. for $C_8H_{17}OCl_3Si$: Cl, 40·4; Si, 10·6%), and (+)-dichlorodi-2-octyloxysilane (5·0 g.), b. p. 118—120°/0·3 mm., α_D^{18} +17·6° [Found : Cl, 20·5; Si, 7·9. Calc. for $(C_8H_{17}O)_2SiCl_2$: Cl, 19·9; Si, 7·84%], were obtained. Formation of 2-chloro-octane was not observed.

(+)-Octan-2-ol (1·95 g., 1 mol.; α_D^{18} +8·0°) in *n*-pentane (5 c.c.) was added to dichloro-(+)-di-2-octyloxysilane (5·36 g., 1 mol.; α_D^{18} +17·6°) in pentane (10 c.c.) at −10°. The solution was allowed to warm to room temperature (1 hour) and dry air was gently aspirated through the liquid, the effluent gas being passed through an absorption tube. After an hour the liquid was distilled, (+)-chlorotri-2-

octyloxysilane (6·0 g., 89%), b. p. 148°/0·2 mm., α_D^{18} +18·32° [Found: Cl, 8·1; Si, 6·1. Calc. for $(C_8H_{17}O)_3SiCl$: Cl, 7·9; Si, 6·2%], being obtained. During the reaction 0·503 g. (Calc.: 0·548 g.) of hydrogen chloride was evolved. There was no indication of the formation of 2-chloro-octane. The trichlorosilane (6·36 g., 1 mol.), pyridine (5·22 g., 3 mol.), and octan-2-ol (8·6 g., 3 mols.) in pentane (35 c.c.) at −10° afforded pyridine hydrochloride (7·0 g. Calc.: 6·98 g.) (Found: Cl, 30·5; C_5H_5N, 68·2%) and the tetra-ester (12·0 g.), b. p. 190°/0·3 mm.

Whilst silicon tetrachloride (4·25 g., 0·25 mol.) in *n*-pentane (10 c.c.) was added dropwise to (+)-octan-2-ol (13·0 g., 1 mol.; α_D^{18} +7·8°) in *n*-pentane (30 c.c.) at −5°, hydrogen chloride was steadily evolved into an absorption tube. After the gentle aspiration of air for 1 hour at 15°, distillation afforded the tetra-ester (12·0 g.), b. p. 190°/0·3 mm., α_D^{18} +17·20° (Found: C, 70·7; H, 12·6%), which was the only distillate after the removal of pentane at 15°/15 mm. The absorption tube contained Cl, 3·02 g. (Calc.: Cl, 3·55 g.). 2-Chloro-octane was not formed.

(+)-1-Phenylethanol (18·3 g., 1 mol.; α_D^{18} +8·84°) dissolved in *n*-pentane (20 c.c.) was added with stirring to silicon tetrachloride (25·5 g., 1 mol.) in pentane (20 c.c.) at −10°. There was a copious evolution of hydrogen chloride, and gelatinous hydrated silica was formed. At the end of the addition, the latter was separated, washed with ethyl alcohol and ether, and dried in air; it then weighed 3·8 g., and corresponded to $SiO_2.H_2O$. From the primary filtrate, 1-chloro-1-phenylethane (13·5 g.), b. p. 73—74°/11 mm., α_D^{18} 0° (Found: Cl, 25·2. Calc. for C_8H_9Cl: Cl, 25·3%), fractions, b. p. 79—89°/11 mm. (2·2 g.), α_D^{18} +1·4° (rapidly gelled in contact with air), and b. p. 98—104°/11 mm. (2·4 g.), α_D^{18} +10·0° (believed to be the trichlorosilane, $RO{\cdot}SiCl_3$), and a residue (1·2 g.) which gelled on cooling, were obtained. The intermediate fractions gelled when kept in sealed tubes. The fraction, b. p. 98—104°/11 mm., after being kept sealed for a year, had separated into two layers, the upper being the racemised chloride, b. p. 73°/12 mm.

When the tetrachloride (2·83 g., 0·25 mol.) in pentane (5 c.c.) was added dropwise with stirring to the (+)-alcohol (8·14 g., 1 mol.; α_D^{18} +8·84°) in pentane (20 c.c.) at −10°, a gelatinous precipitate of hydrated silica was formed at each addition. After a further 30 minutes the mixture was filtered, and from the filtrate, by direct distillation, (−)-1-chloro-1-phenylethane (7·5 g.), b. p. 73°/12 mm., α_D^{18} −3·72° (Found: Cl, 25·1. Calc. for C_8H_9Cl: Cl, 25·3%), was obtained, but no silicon compounds were detected. The actual formation of chloride was much greater than recorded above (80%); the precipitated silica adsorbs the product, and considerable volumes of ethyl alcohol and ether were required to free the silica from adsorbed material. The leaching liquids were not incorporated with the primary filtrate. From the weight of hydrated silica ($SiO_2.H_2O$) (1·20 g. Calc.: 1·30 g.) the amount of chloride formed was 92%.

Silicon tetrachloride (8·5 g., 0·25 mol.) in pentane (10 c.c.) was added dropwise to *tert.*-amyl alcohol (17·6 g., 1 mol.) in pentane (30 c.c.) at −10°. Apparently, there was no reaction, not even at 0°; but at room temperature a reaction became vigorous and was difficult to control. Hydrated silica (3·57 g. Calc.: $SiO_2.H_2O$, 3·90 g.) separated and was treated as described above. The filtrate afforded *tert.*-amyl chloride (15 g.), b. p. 85° (Found: Cl, 33·3. Calc. for $C_5H_{11}Cl$: Cl, 33·3%), but there was loss of product during fractionation. Based on weight of the hydrated silica the formation of the chloride was 91·5%.

Silicon tetrachloride (4·25 g., 0·25 mol.) in xylene (10 c.c.) was added with stirring to *tert.*-butyl alcohol (7·4 g., 1 mol.) in xylene (20 c.c.). Again reaction was slow in commencing even at 18°, and only at 40° did the reaction show obvious signs of occurrence; then it rapidly became vigorous. Analogously with the foregoing, hydrated silica (1·87 g. Calc.: 1·95 g.) and *tert.*-butyl chloride (6·7 g.), b. p. 51° (Found: Cl, 38·1. Calc. for C_4H_9Cl: Cl, 38·4%), were obtained.

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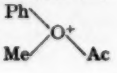
111. *Acylation Reactions catalysed by Strong Acids. Part III. The Acetylium Ion as a Debenzylating Agent.*

By H. BURTON and P. F. G. PRAILL.

Benzyl phenyl ether forms an oxonium salt with the acetylium ion and the subsequent reactions of the benzyl cation arising by decomposition of the oxonium ion are followed by investigating the products formed in various solvents. Suitably constituted aryl benzyl ethers are shown to be largely debenzylated by treatment with a little 72% perchloric acid in acetic anhydride. The benzyl group is removed as benzyl acetate and the acetate of the phenol results. Sulphuric acid is less effective than perchloric acid for the same purpose.

IN view of the well-known tendency for ethers to undergo oxonium salt formation, it was necessary in Part I (*J.*, 1950, 1203) to point out that in the reaction between anisole and acetylium perchlorate the experimental results indicated that formation of the ion,



could have occurred only to a very limited extent. We expressed the view that this ion could not be expected to undergo a Friedel–Crafts type of reaction with the acetylium ion (Ac^+), but we did consider that an oxonium ion of this type might be expected to undergo an " acetolysis " in the presence of acetic anhydride, namely :

$$PhO^+MeAc + Ac_2O \longrightarrow PhOAc + MeOAc + Ac^+$$

This reaction would clearly result in the regeneration of acetylium ion, and if realisable should consequently give valuable evidence of the catalytic nature of the acetylium ion in such processes. The only evidence adduced (*loc. cit.*) for such an acetolysis was that extraction of the reaction product from anisole and acetylium perchlorate with cold aqueous sodium hydroxide gave small but definite amounts of phenol, undoubtedly formed by hydrolysis of a little phenyl acetate.

We did not wish to imply in Part I (*loc. cit.*) that addition of the acetylium ion to the ethereal oxygen was a limited process but rather that the overall reaction resulted in the setting up of an equilibrium, $PhOMe + Ac^+ \rightleftharpoons PhO^+MeAc$, lying well to the left. We consider that such an oxonium ion once formed could equally readily eliminate the acetylium ion to regenerate the original reactants. In our view both processes would be of comparable facility and consequently the final nature of any subsequent reaction would not be affected to any appreciable extent.

In order to see if we could increase the stability of the ion, or, in other words, displace the above equilibrium from the left towards the right for a similarly constituted oxonium ion we investigated the reaction between acetylium perchlorate and benzyl phenyl ether. The greater electron-donating property of the benzyl group (as compared with methyl), which is apparent from the well-known fact that debenzylation is a much more facile process than demethylation of the corresponding aryl ethers, should facilitate the decomposition of the oxonium ion, $CH_2Ph{\cdot}O^+PhAc$, which we should expect, if formed to any appreciable extent, to undergo characteristic fission. We surmised that benzyl phenyl ether would add acetylium much more readily than anisole and that once formed, it would give, ***inter alia***, more positive evidence of an acetolysis reaction of the type discussed above. To avoid the possible complications of acetic acid in the reaction mixtures we decided in the first place not to use an acetic anhydride–perchloric acid mixture but to apply our technique (*J.*, 1950, 2034) of using acetyl chloride and silver perchlorate in an inert solvent of relatively high dielectric constant, namely, nitromethane. We found that, with equimolecular amounts of the reagents and generation of the acetylium perchlorate in the presence of all the ether, the reaction product was a mixture containing (as indicated by normal qualitative tests) only a trace of benzyl ether, and also small amounts of ketonic material (since treatment of the reaction product with Brady's reagent resulted in a marked, red coloration). At first we were of the opinion that these observations indicated that the reaction

$$CH_2Ph{\cdot}OPh + Ac^+ \longrightarrow CH_2Ph{\cdot}O{\cdot}C_6H_4{\cdot}COMe + H^+$$

might possibly be occurring to a very minor degree, although we could not reconcile this view with the fact that the reaction product gave an almost negative test for the benzyl ether grouping with hot concentrated hydriodic acid. We were compelled therefore to consider that any ketone formed could not be *p*-benzyloxyacetophenone, which we found (see Experimental) gave a very characteristic, insoluble 2 : 4-dinitrophenylhydrazone and which, even in small amount, also gave the characteristic smell of benzyl iodide when treated with hydriodic acid. We were fortunate in one experiment (of several carried out in nitromethane as solvent) to isolate a small but definite amount of a crystalline 2 : 4-dinitrophenylhydrazone which from its composition and physical and chemical properties was almost certainly *p*-hydroxyacetophenone 2 : 4-dinitrophenylhydrazone. The formation of very small amounts of ketone, irrespective of the structure of the product, was in marked contrast to the results obtained with anisole and acetylium perchlorate, which under identical conditions gave at least 84% of *p*-methoxyacetophenone, and indicated quite clearly that the reaction mechanism for the benzyl ether was taking a different course.

We proved that the reaction product did in fact contain a fair amount (at least 0·22 mol.) of phenyl acetate together with a larger quantity of a higher-boiling product, the composition and molecular weight of which approximated to those of a benzylphenyl acetate and which on this formulation resulted to the extent of at least 0·38 mole. In addition, an appreciable amount of a still more complex product was also found but this was not investigated further owing to its intractable nature. The possibility that this last product was formed by the condensation of *p*-benzyloxyacetophenone produced (as above) appeared to us to be excluded by the fact that no appreciable reaction for the benzyl ether group was observed.

We concluded from the experiments carried out under these conditions that the following reactions had occurred :

$$CH_3Ph{\cdot}OPh + Ac^+ \rightleftharpoons CH_3Ph{\cdot}O^+PhAc \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$CH_3Ph{\cdot}O^+PhAc \longrightarrow PhOAc + {}^+CH_2Ph \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$PhOAc + {}^+CH_2Ph \longrightarrow CH_3Ph{\cdot}C_6H_4{\cdot}OAc + H^+ \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$PhOAc + Ac^+ \longrightarrow COMe{\cdot}C_6H_4{\cdot}OAc + H^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

In addition it may be that further reaction of the benzylphenyl acetate with benzyl cations had also taken place. Alternatively, it might be possible that " polymerisation " of some of the benzyl cations had occurred in the manner suggested by Monicelli and Hennion (*J. Amer. Chem. Soc.*, **1941**, **63**, 1722), *viz.* :

$$n{}^+CH_2Ph \longrightarrow (CHPh)_n + nH^+$$

but we put forward this suggestion with considerable reserve.

We showed that the properties of the " benzylphenyl acetate " were in accordance with our formulation but we did not think it worth while or necessary to see if it was a mixture of *o*- and *p*-isomerides. It is also clear that the almost negative test for the benzyloxy-group also excludes the unlikely possibility that the decomposition

$$CH_3Ph{\cdot}O^+PhAc \longrightarrow CH_3Ph{\cdot}OAc + Ph^+$$

had taken place.

We have formulated reaction (3) in the above manner because we do not wish to imply that the benzylphenyl acetate arises as a result of an intramolecular reaction

$$CH_3Ph{\cdot}O^+PhAc \longrightarrow CH_3Ph{\cdot}C_6H_4{\cdot}OAc + H^+$$

which would involve a migration of the benzyl group. We show in our subsequent discussion that such a rearrangement is excluded.

The above results are in some respects similar to those obtained by Monicelli and Hennion (*loc. cit.*) on the decomposition of, *e.g.*, benzyl propyl ether by boron trifluoride. In the latter case, however, the reaction mechanism is clearly different since the neutral ether and boron trifluoride give a benzyl cation and a complex anion :

$$CH_3Ph{\cdot}OPr + BF_3 \longrightarrow {}^+CH_2Ph + [BF_3{\cdot}OPr]^-$$

Proof of the formation of the benzyl cation was given (*loc. cit.*) by carrying out the decomposition in presence of various solvents, but we wish to mention two in particular, benzene and acetic anhydride, since the results obtained by Monicelli and Hennion are pertinent to our subsequent work. The formation of diphenylmethane in benzene as a solvent clearly establishes the production of the benzyl cation and its high reactivity. On the other hand, we are extremely surprised that in the presence of acetic anhydride as a solvent no benzyl acetate was produced : we should predict that this would have been formed to the same extent as propyl acetate by the reaction :

$${}^+CH_2Ph\,[BF_3{\cdot}OPr]^- + Ac_2O \longrightarrow CH_3Ph{\cdot}OAc + PrOAc + BF_3$$

It is possible that the reaction does take this course and that the regenerated boron trifluoride reacts preferentially with the benzyl acetate to give the so-called polymerised product (*loc. cit.*).

Our reasons for postulating reaction (4) are supported by the behaviour of *p*-benzyloxyacetophenone towards acetylium perchlorate in nitromethane. The ketone is not debenzylated to any appreciable extent but does undergo partial conversion into an orange compound exhibiting a marked green fluorescence in alcoholic solution. This compound is clearly of the same type as that produced from *p*-methoxyacetophenone under similar conditions (see Parts I and II). We surmise that the method used for isolation of the reaction product in our first series of experiments, together with the use of alcoholic sulphuric acid for the preparation of the 2 : 4-dinitrophenylhydrazone, did in fact lead to hydrolysis of the original acetoxy-group.

We do not consider that the stability of the benzyloxy-group in *p*-benzyloxyacetophenone towards the acetylium ion vitiates any of our results, because it must be apparent that in the structure, $COMe{\cdot}C_6H_4{\cdot}O{\cdot}CH_2Ph$, the carbonyl oxgen atom would be expected to undergo more ready addition of acetylium than the ethereal oxygen and so lead, in the first place, to the formation of the ion, $CH_3Ph{\cdot}O{\cdot}C_6H_4{\cdot}C^+Me{\cdot}OAc$. We think it very probable that an ion of this type is involved in the production of the coloured compound exhibiting fluorescence. This and the similar compounds formed in the reaction between anisole and acetylium perchlorate,

especially in the presence of acetic anhydride, are undoubtedly pyrylium salts of the type obtained by Dilthey (*J. pr. Chem.*, 1916, [ii], **94**, 75) from, for example, *p*-methoxyacetophenone, acetic anhydride, and various catalysts (all of which would be expected to produce acetylium ions). We have found in all our experiments with anisole and with benzyl phenyl ether that if *C*-acetylation does occur to any appreciable extent then the reaction mixture on treatment with water and ether generally shows a green fluorescence.

We have found when acetylium perchlorate and benzyl phenyl ether are allowed to react in benzene as the solvent that phenyl acetate, the fraction corresponding to benzylphenyl acetate, and diphenylmethane are all produced. The isolation of diphenylmethane indicates clearly that the possibility of an intramolecular reaction as discussed above (p. 524) is untenable since the benzyl cation produced in equation (2) reacts with both phenyl acetate and the benzene. In this experiment it is clear that reactions (1), (2), (3), possibly (4) (see Experimental) and also the reaction

$$^{+}CH_2Ph + C_6H_6 \longrightarrow CH_2Ph_2 + H^{+}$$

have occurred.

Our formulation of an " acetolysis " reaction of the type first mentioned (p. 523) in this paper should clearly be capable of proof if the reaction between acetylium perchlorate and benzyl phenyl ether were carried out in the presence of an excess of acetic anhydride, since the following reactions could occur in addition to (1), (2), (3), and (4) :

$$CH_2Ph{\cdot}O^{+}PhAc + Ac_2O \longrightarrow CH_2Ph{\cdot}OAc + PhOAc + Ac^{+} \quad (5)$$

(or $$^{+}CH_2Ph + Ac_2O \longrightarrow CH_2Ph{\cdot}OAc + Ac^{+}) \quad (5a)$$

and $$CH_2Ph{\cdot}OPh + Ac^{+} \longrightarrow CH_2Ph{\cdot}O{\cdot}C_6H_4{\cdot}COMe + H^{+} \quad (6)$$

Since reaction (5) or (5*a*) regenerates acetylium ions, and reactions (3), (4), and (6) produce hydrogen ions which are known (Parts I and II) to give acetylium ions in the presence of acetic anhydride, it is clear that these conditions should all tend to maintain a high concentration of acetylium in the reaction mixture. If *C*-acetylation of the neutral benzyl phenyl ether can occur it must be apparent that reaction (6) is thus capable of being realised. We have shown that the ether (1 mol.) and acetylium perchlorate (0·5 mol.) in the presence of acetic anhydride (2 mols.) diluted with nitromethane give a complex reaction mixture containing *p*-benzyloxyacetophenone, phenyl acetate, benzyl acetate, and the benzylphenyl acetate fraction, all of which have been identified.

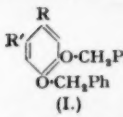
It is apparent from these results that reaction (1) clearly leads, as expected, to an equilibrium. Our initial experiments, *i.e.*, in nitromethane alone, and those in benzene, were so carried out that an excess of the benzyl phenyl ether was present in the first half of the reaction and our results are in accordance with this procedure. The constant regeneration of acetylium ions in the experiment using acetic anhydride–nitromethane as the solvent indicates that the free ether is necessary for the Friedel–Crafts type of reaction to take place. It must also be apparent that reactions (1) (*et seq.*) and (6) occur at markedly different rates and it would be expected that the latter would be the slower. All our results prove that such is the case. They also indicate quite definitely that the benzyl cation is an extremely reactive entity and far exceeds the reactivity of the acetylium ion. We attach considerable importance to this marked difference in reactivity since we feel that the alkylation and acylation of aromatic compounds by the Friedel–Crafts procedure are not strictly comparable. We propose to elaborate this thesis in a subsequent paper.

We did also carry out one experiment in which the benzyl phenyl ether was added to the pre-formed acetylium perchlorate. Under these conditions, *i.e.*, an excess of acetylium ion present in the first 50% of the reaction, a non-distillable reaction product resulted. This result was not unexpected since the intermediate phenyl acetate must be attacked by acetylium and benzyl cation.

It has been stated by Roberts and Hammett (*J. Amer. Chem. Soc.*, 1937, **59**, 1063; cf. Clark and Todd, *J.*, 1950, 2030) that the benzyl cation is probably yellow. It is true that in our experiments involving the benzyl cation a yellow colour usually developed in the first instance; we have also remarked (Parts I and II) on the development of a similar yellow colour in solutions containing acetylium perchlorate. We find, however, that in the presence of ethers in particular there is usually an intensification of the original yellow colour to sometimes intense shades of purple. It may well be that the benzyl and acetyl cations are both yellow but we would not attach undue importance to this, since the production of colour appears to

us to depend partly on the medium in which the reaction is carried out and largely on the nature of the compound produced in the reaction.

It will be apparent from the reactions postulated above leading to the regeneration of acetylium or hydrogen ions, that mixtures of perchloric acid and an excess of acetic anhydride should be capable of debenzylating suitably constituted benzyl ethers, and also that the process should be catalytic as far as the perchloric acid is concerned. We have shown that benzyl phenyl ether treated under these conditions gives the same simpler products as our last series of experiments. The qualitative differences can be ascribed to the rather different composition of the reaction mixture since the use of aqueous perchloric acid must lead to the formation of acetic acid. It is noteworthy that, under the conditions we have actually used, a little unchanged ether could be isolated; this was not observed in any of the other series of experiments. The formation of the more complex products was actually less. Encouraged by this result we decided to investigate this catalytic debenzylation process with three dibenzyl ethers of the general formula (I) which had been prepared in connection with another investigation. In each case the group R was nitro- or formyl whilst in two cases R′ was hydrogen and in the third methyl. We selected these structural conditions deliberately since there appeared to us to be no possibility of nuclear acetylation in these cases. We found that 3 : 4-dibenzyloxybenzaldehyde (protocatechualdehyde dibenzyl ether) (I; R = CHO, R′ = H) gave a good yield of 3 : 4-diacetoxybenzylidene diacetate which was also similarly obtained from protocatechualdehyde itself. Similarly, 3 : 4-dibenzyloxy-1-nitrobenzene (4-nitrocatechol dibenzyl ether) (I; R = NO_2, R′ = H) gave mainly 4-nitrocatechol diacetate, or the monoacetate monobenzyl ether according to the conditions used, but the analogous 4 : 5-dibenzyloxy-2-nitrotoluene (I; R = NO_2, R′ = Me) gave mainly 4(or 5)-acetoxy-5(or 4)-benzyloxy-2-nitrotoluene. This last result may be a consequence of the electron-repelling methyl group and we think it would be worth while to study this effect in due course. In the meantime we feel that our results give valuable support to the various reactions postulated in this communication.



(I.)

In Part I (*loc. cit.*) we also suggested that concentrated sulphuric acid in an excess of acetic anhydride should also give rise to acetylium ions :

$$Ac_2O + H_2SO_4 \rightleftharpoons Ac^+ + AcOH + HSO_4^-$$

A proof of the correctness of this suggestion has recently been supplied by Gillespie (*J.*, 1950, 2997) who has shown, by cryoscopic measurements, that acetic (and benzoic) anhydride in an excess of sulphuric acid reacts completely as follows :

$$Ac_2O + 2H_2SO_4 \longrightarrow Ac^+ + AcOH_2^+ + 2HSO_4^-$$

The well-known fact that such mixtures undergo mutual interaction to produce sulphoacetic acid also appeared to be manifest in Gillespie's experiments. Our view that the sulphuric acid–acetic anhydride mixture would not be such an effective source of acetylium ions as the perchloric acid–acetic anhydride mixture appears to us to be well substantiated by our finding that 3 : 4-dibenzyloxy-1-nitrobenzene was converted under comparable reaction conditions, by a little sulphuric acid in acetic anhydride into a 4-nitrocatechol acetate monobenzyl ether without any trace of 4-nitrocatechol diacetate. Similarly 3 : 4-dibenzyloxybenzaldehyde gave a triacetate which was undoubtedly 3(or 4)-acetoxy-4(or 3)-benzyloxybenzylidene diacetate, $CH_2Ph{\cdot}O{\cdot}C_6H_3(OAc){\cdot}CH(OAc)_2$. These results show, however, in spite of the differences, that debenzylation with concentrated sulphuric acid in acetic anhydride does occur. We did not investigate the orientation of the acetoxy- and benzyloxy-groups in these mixed ether acetates.

Incidental to this investigation we have examined, in the first instance in collaboration with Dr. J. L. Stoves, the nitration of *o*-dibenzyloxybenzene (catechol dibenzyl ether) and find, as with veratrole, that this leads exclusively to substitution in the 4-position of the original benzene ring. The constitution of the resulting 3 : 4-dibenzyloxynitrobenzene (4-nitrocatechol dibenzyl ether) was proved by its ready debenzylation by hydrobromic acid to 4-nitrocatechol which was further identified as its diacetate and also as its dimethyl ether (4-nitroveratrole).

We have found dioxan to be a very convenient medium for the preparation of aryl benzyl ethers in spite of the reaction being generally slower than when alcohol is used as the solvent. The main advantage is that the resulting product is not contaminated with benzyl ethyl ether.

Experimental.

Materials.—Acetyl chloride and benzene were AnalaR reagents. Silver perchlorate was treated as described in Part II (*J.*, 1950, 2034).

Benzyl Phenyl Ether.—Potassium hydroxide (0·67 g.-mol.) in water (38 c.c.) was added to phenol (0·67 g.-mol.) in dioxan (500 c.c.), and the resulting solution was heated on a steam-bath. Benzyl

chloride (0·67 g.-mol.) was added during 30 minutes and the resulting heterogeneous mixture was heated and stirred for 36 hours. About two-thirds of the solvent was removed in a vacuum and the residue poured into water (*ca.* 1·2 l.). After extraction with ether the combined ethereal extracts were washed with 2N-sodium hydroxide until the washings no longer became opaque on acidification. The residue from the dried (Na_2SO_4) ethereal extract gave a fraction (*ca.* 50%), b. p. 160—165°/12 mm., which solidified on cooling. Crystallisation from alcohol gave colourless flakes, m. p. 38—39°.

p-*Benzyloxyacetophenone.*—The spongy mass of yellow solid precipitated on addition of potassium hydroxide (4·5 g.) in water (4·5 c.c.) to a solution of *p*-hydroxyacetophenone (9·6 g.) in dioxan (100 c.c.) was heated on a steam-bath and benzyl chloride (10·1 g.) was added. After refluxing gently for 15—16 hours the mixture was added to water (750—800 c.c.). The light-brown waxy solid which precipitated was dissolved in ether, and the solution washed thrice with 2N-sodium hydroxide and then with water. The dried (Na_2SO_4) ethereal solution was evaporated, excess of dioxan being removed in a vacuum. The *ketone* crystallised from methyl alcohol in pale cream-coloured needles (9·1 g.), m. p. 88°. Recrystallisation from benzene gave almost colourless prisms, m. p. 91—92° (Found : C, 79·6; H, 6·3. $C_{15}H_{14}O_2$ requires C, 79·6; H, 6·2%). *p*-Hydroxyacetophenone (1·6 g.) was recovered from the alkaline washings.

The 2 : 4-*dinitrophenylhydrazone* separated in deep crimson flakes, m. p. 188—190°, from ethyl acetate (Found : C, 62·1; H, 4·5; N, 13·8. $C_{21}H_{18}O_5N_4$ requires C, 62·1; H, 4·4; N, 13·8%).

Fission of Benzyl Phenyl Ether with Acetylium Perchlorate.—In nitromethane. (*a*) Acetyl chloride (0·05 g.-mol.) was added during 15 minutes to a cold (0—5°) solution of benzyl phenyl ether (0·05 g.-mol.) and silver perchlorate (0·05 g.-mol.) in nitromethane (104 g.). The mixture was kept for a further 30 minutes at 0—5°, and the silver chloride was filtered off from the mauve solution, the filtrate being allowed to drop on crushed ice. After washing of the silver chloride with ether, the combined ethereal nitromethane solution was separated and washed repeatedly with water until the washings were no longer acid (Congo-red). After evaporation of the dried (Na_2SO_4) solution, the residue was separated by distillation in a vacuum into the fractions : (i) b. p. 77—80°/8 mm. (1·7 g.), which redistilled at 190—194° under atmospheric pressure ; (ii) b. p. 160—180°/6—8 mm. (4·3—4·4 g.); (iii) b. p. 200—250°/4 mm. (1·4—1·8 g.); and (iv) a residue (2—3 g.).

Fraction (i) consisted of phenyl acetate, confirmed by hydrolysis with boiling 2N-sodium hydroxide to phenol which was liberated by carbon dioxide (general procedure) and identified (standard procedure) as 2 : 4 : 6-tribromophenol, m. p. and mixed m. p. 91°. No evidence for the presence of benzyl acetate (see p. 528) was obtained.

Fraction (ii) (Found : C, 81·1; H, 6·2%; *M*, 255. Calc. for $C_{15}H_{14}O$: C, 79·6; H, 6·2%; *M*, 226), a viscous pale yellow oil, did not yield any crystalline material when kept. It gave an intense red colour with cold, alcoholic 2 : 4-dinitrophenylhydrazine sulphate but on one occasion only was crystalline material (0·3 g.) deposited. This crystallised from ethyl acetate in dark red needles, m. p. 255° (decomp.) (Found : C, 53·4; H, 4·1; N, 17·7. Calc. for $C_{14}H_{12}O_4N_4$: C, 53·2; H, 3·8; N, 17·7%), which did not depress the m. p. of genuine *p*-hydroxyacetophenone 2 : 4-dinitrophenylhydrazone, m. p. 254° (decomp.), and was readily soluble in cold, dilute sodium hydroxide. Vogel (" Practical Organic Chemistry," Longmans, Green & Co., 1948, p. 706) gives m. p. 261° for this 2 : 4-dinitrophenylhydrazone.

Hydrolysis of fraction (ii) with boiling 2N-sodium hydroxide for 2 hours gave a little insoluble, dark-coloured oil together with mainly phenolic material which could not be induced to crystallise.

Oxidation of the original material (fraction ii) with chromic oxide in warm glacial acetic acid gave an ether-soluble product which with hot alcoholic 2 : 4-dinitrophenylhydrazine sulphate—the condition necessary for 2 : 4-dinitrophenylhydrazone formation from benzophenone and substituted benzophenones—afforded a deep-red solution smelling strongly of ethyl acetate (ethanolysis of the acetoxy-group), from which solid matter separated slowly. This was obviously a mixture and may have consisted of at least *o*- and *p*-acetoxy- and *o*- and *p*-hydroxy-benzophenone 2 : 4-dinitrophenylhydrazones.

Fraction (iii) was a very viscous yellow oil which did not crystallise on being kept.

The residue was a viscous brown gum.

None of the fractions gave more than the merest trace of benzyl iodide when treated with boiling hydriodic acid (*d* 1·7) in acetic acid.

(*b*) When the reaction was carried out by adding the solution of benzyl phenyl ether in nitromethane to the prepared acetylium perchlorate also in nitromethane the main product was a non-distillable gum. No ketonic material could be isolated.

(*c*) *In benzene.* The reaction described under (*a*) was repeated, but in benzene (260 c.c.) instead of nitromethane as the solvent and at 5°. The following fractions were obtained : (i) B. p. 192—194° (2·2 g.), which was shown (as above) to be phenyl acetate. (ii) B. p. 68—95° (mainly 92—95°)/3·5—4·5 mm. (4·0 g.), a mixture of phenyl acetate and diphenylmethane in the ratio of 1 : 3. The diphenylmethane was separated from the phenyl acetate by treatment of the mixture with boiling 2N-sodium hydroxide and subsequent extraction of the alkaline mixture with ether; it crystallised in long colourless needles, m. p. 25°, and was readily oxidised by chromic oxide in warm acetic acid to benzophenone which was identified as its 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 229°. (iii) B. p. 95—120°/3—4 mm. (0·9 g.). (iv) B. p. 120—150° (mostly 135—140°)/4 mm. (3·0 g.). The residue (1·2 g.) was a dark gum.

None of the fractions nor the residue gave more than a trace of benzyl iodide with boiling hydriodic acid. Only fraction (iv) gave an indication that a trace of ketonic material might be present.

(*d*) *In acetic anhydride.* A solution of silver perchlorate (0·025 g.-mol.) and benzyl phenyl ether (0·05 g.-mol.) in acetic anhydride (0·1 g.-mol.) and nitromethane (57·2 g.) was cooled to 0—5°. Acetyl chloride (0·025 g.-mol.) was added with shaking to the cooled solution during 15 minutes and the resultant mixture kept at 0—5° for 45 minutes. The product was isolated as described in (*a*) : in this case the ethereal extracts had a strong green fluorescence. Fractionation gave : (i) A liquid, b. p. 195—198°

(3·6 g.), a mixture of phenyl acetate and benzyl acetate in the approximate ratio of 7 : 1. Hydrolysis of the mixed product with boiling 2N-sodium hydroxide and extraction of the alkaline mixture with ether gave a little oil which was identified as benzyl alcohol by oxidation with boiling aqueous potassium permanganate to benzoic acid, m. p. and mixed m. p. 121°. The alkali-soluble material gave phenol. (ii) A small (1·1 g.) fraction, b. p. 100—180°/7·5—8 mm., which was not further investigated. (iii) A fraction, b. p. 190—205°/8—9 mm. (2·6 g.), which solidified on cooling and consisted mainly of *p*-benzyloxyacetophenone, m. p. 86—87°, which did not depress the m. p. of the synthetic ketone. (iv) Material, b. p. 205—260°/8—9 mm. (2·4 g.), consisting of an oil from which a little crystalline material slowly separated. The residue from the fractional distillation amounted to 1·0 g.

3 : 4-*Dibenzyloxybenzaldehyde* (*Protocatechualdehyde Dibenzyl Ether*).—Potassium hydroxide (0·2 g.-mol.) in water (12 c.c.) was cautiously added to a solution of protocatechualdehyde (0·1 g.-mol.) and benzyl chloride (0·2 g.-mol.) in ethyl alcohol (100 c.c.). The mixture was then refluxed until neutral to litmus and then poured into water. The crude *aldehyde*, which separated as a pale yellow solid, crystallised from ethyl alcohol in clusters of almost colourless needles, m. p. 91° (Found : C, 79·3; H, 5·6. $C_{21}H_{18}O_3$ requires C, 79·2; H, 5·7%).

3 : 4-*Diacetoxybenzylidene Diacetate*.—A solution of protocatechualdehyde (10 g.) in warm acetic anhydride (100 c.c.) was cooled to room temperature and then treated with 72% perchloric acid (0·25 c.c.), the mixture becoming warm. After 30 minutes the solution was poured into ice-water, and the crude product filtered off and recrystallised from ethyl alcohol (96%), giving the tetra-acetate (18·8 g.), m. p. 131° (Found : C, 55·7; H, 5·3. Calc. for $C_{18}H_{18}O_8$: C, 55·6; H, 5·0%).

o-*Dibenzyloxybenzene* (*Catechol Dibenzyl Ether*).—A solution of sodium hydroxide (20 g.) in water (150 c.c.) was gradually added to a boiling solution of catechol (27·5 g.) and benzyl chloride (70 c.c.) in ethyl alcohol (300 c.c.), and the mixture then refluxed for 8 hours. The oil which separated solidified when kept overnight. The ether crystallised from light petroleum (b. p. 40—60°) in colourless prisms (32·5 g.), m. p. 61·5°.

3 : 4-*Dibenzyloxy*-1-*nitrobenzene* (4-*Nitrocatechol Dibenzyl Ether*).—o-Dibenzyloxybenzene (10 g.) was dissolved in warm glacial acetic acid (100 c.c.) and the solution cooled to 20—25°. Nitric acid (*d* 1·4; 10 c.c.) was then added gradually with stirring so that the temperature did not exceed 25°; a yellow solid separated during the reaction. The mixture was diluted with water and the crude nitro-ether crystallised from a large volume of ethyl alcohol from which it separated in needles (yield, 96—100%), m. p. 97·5° (Found : N, 4·2. Calc. for $C_{20}H_{17}O_4N$: N, 4·2%). Balaban (*J.*, 1929, 1092) gives m. p. 97° for this ether prepared from 4-nitrocatechol.

A mixture of the nitro-ether (10·1 g.), 50% hydrobromic acid (50 c.c.), and acetic acid (75 c.c.) was boiled under reflux for 6—7 hours. The mixture, from which a dark oil separated, was evaporated to dryness in a vacuum and the residue was extracted with boiling water (100 c.c.), in the presence of charcoal. Evaporation of the filtered extract to *ca.* 20 c.c. gave, on cooling, yellow needles (2·4 g.) which when recrystallised from water separated in long yellow needles, m. p. 174—175° (decomp.). 4-Nitrocatechol has m. p. 176° (decomp.) (Cardwell and Robinson, *J.*, 1915, **107**, 258).

4-Nitrocatechol (1·6 g.), dissolved in acetic anhydride (16 c.c.), was treated with 72% perchloric acid (2 drops). The mixture, which became warm (35—40°), was left for 30 minutes and then poured on crushed ice. The crude diacetate crystallised from ethyl alcohol in colourless needles, m. p. 84° (Found : C, 50·4; H, 4·1. Calc. for $C_{10}H_9O_6N$: C, 50·2; H, 3·8%).

The diacetate is reported (Balaban, *loc. cit.*) to have m. p. 98° when prepared from 4-nitrocatechol by the action of acetic anhydride–sulphuric acid. We have not been able to attain this m. p. (see also p. 529) even after repeated crystallisation.

Methylation of the nitrocatechol with methyl sulphate and aqueous sodium hydroxide gave 4-nitroveratrole, m. p. and mixed m. p. 96°.

Debenzylations with a Small Amount of 72% *Perchloric Acid in Acetic Anhydride*.—(*a*) Benzyl phenyl ether (4·6 g.) in acetic anhydride (10·2 g.) was treated with 72% perchloric acid (2 drops), the resultant deep orange-red mixture being kept below 27° by cooling. After 30 minutes the reaction mixture was poured on crushed ice (*ca.* 40 g.). Most of the colour then slowly disappeared but a strong green fluorescence was evident. During extraction of the oily product with ether a small amount of a light brown solid material separated; this was sparingly soluble in alcohol, giving a yellow solution with an intense green fluorescence. The combined ethereal extracts were washed with 5% sodium hydrogen carbonate solution and with water. Evaporation of the dried (Na_2SO_4) ethereal solution gave an oil which was separated by vacuum distillation into the following fractions : (i) b. p. 70—80°/8 mm. (1·0 g.), an 8 : 1 mixture of phenyl acetate and benzyl acetate; (ii) b. p. 120—140°/9 mm. (0·9 g.), containing some phenyl acetate, some benzyl acetate, and some unchanged ether, since redistillation at atmospheric pressure gave approximately equal amounts of the mixed acetates, b. p. *ca.* 210°, and a residue of unchanged ether; (iii) b. p. 140—150°/9 mm. (1·0 g.), which solidified on cooling and was unchanged ether (m. p. and mixed m. p.); (iv) b. p. 150—200° (mainly 180—190°)/6—7 mm. (1·0 g.), which also solidified on cooling and was *p*-benzyloxyacetophenone (m. p. and mixed m. p.). The residue from the distillation amounted to 1·1 g.

(*b*) 3 : 4-Dibenzyloxybenzaldehyde (1·0 g.) in acetic anhydride (3 c.c.) was treated with 72% perchloric acid (2 drops), whereupon a dark green solution resulted. After 30 minutes the mixture was added to water (25 c.c.) and left for 18 hours at 0°. The aqueous layer was decanted from the semi-solid material, which smelled strongly of benzyl acetate. Dissolution of the paste in the minimum amount of boiling 96% alcohol and keeping at 0° gave crystalline material (0·64 g.), m. p. *ca.* 116°, which when recrystallised from alcohol and benzene gave colourless needles, m. p. 131°, unaltered by admixture with 3 : 4-diacetoxybenzylidene diacetate.

A small amount of material, m. p. 157—159°, was obtained from the crystallisation liquors which was identical with the compound obtained from the debenzylation with sulphuric acid (see below).

(*c*) 3 : 4-Dibenzyloxy-1-nitrobenzene (1·0 g.) in acetic anhydride (3 c.c.) was treated with 72% perchloric acid (2 drops). After 30 minutes the pale green mixture was added to water (25 c.c.) and left at 0° for 18 hours. The aqueous layer was decanted from the resulting pasty mass, which on dissolution in the minimum amount of hot ethyl alcohol and cooling gave colourless needles (0·52 g.), m. p. *ca.* 99°. Recrystallisation from alcohol or benzene–light petroleum gave colourless needles, m. p. 105—106° (Found : C, 62·9; H, 4·3. $C_{15}H_{13}O_5N$ requires C, 62·9; H, 4·5%), of presumably ***4-nitrocatechol acetate benzyl ether.***

In another experiment 3 : 4-dibenzyloxy-1-nitrobenzene (6·7 g.) in acetic anhydride (40 c.c.) was kept below 20° whilst 72% perchloric acid (1·4 g. ≡0·01 mol.) was added cautiously. The mixture was kept at room temperature for 17—18 hours and was then poured into ice-water (*ca.* 250 c.c.), whereupon most of the original deep orange colour disappeared. The oily material was washed once with water and was then dissolved in a small quantity of ethyl alcohol. On this solution being kept, solid material (3·0 g.) separated. This consisted of two types of crystal : (i) a major fraction of large diamond-shaped plates which crystallised well from benzene–light petroleum, had m. p. 85°, and were identical with 4-nitrocatechol diacetate (see p. 528) ; (ii) small needles, which on recrystallisation from benzene–light petroleum proved to be identical with the monoacetate obtained previously (m. p. and mixed m. p. 105—106°).

Distillation of the oily material recovered from the mother-liquors gave benzyl acetate (2·5 g.), b. p. 214—216°, and some tarry residue.

(*d*) 72% Perchloric acid (2 drops) was added to 4 : 5-dibenzyloxy-2-nitrotoluene (1·0 g.) in acetic anhydride (3 c.c.). After 30 minutes the orange-brown mixture was treated with water (25 c.c.) ; a strong smell of benzyl acetate was apparent. The mixture was kept at 0° for 18 hours and the semi-solid material which separated then dissolved in the minimum amount of hot ethyl alcohol. On this solution being kept, light brown needles (0·65 g.), m. p. *ca.* 126°, separated. Recrystallisation from alcohol gave colourless needles of the ***monoacetate monobenzyl ether***, m. p. 133° (Found : C, 63·7; H, 4·9. $C_{16}H_{15}O_5N$ requires C, 63·8; H, 5·0%).

Debenzylations with a Small Amount of Concentrated Sulphuric Acid in Acetic Anhydride.—(*a*) 3 : 4-Dibenzyloxybenzaldehyde (0·5 g.) in acetic anhydride (1·5 c.c.) was treated with concentrated sulphuric acid (2 drops) and after 30 minutes the mixture was decomposed with water. The crude product (0·2 g.), isolated as above, crystallised from alcohol or benzene–light petroleum in colourless needles, m. p. and mixed m. p. 157—159° (Found : C, 65·1; H, 5·4. $C_{20}H_{20}O_7$ requires C, 64·5; H, 5·4%).

In another experiment only the merest trace of sulphuric acid was used and the mixture was kept for 1—2 minutes. The product (0·2 g.) was the almost pure triacetate, m. p. and mixed m. p. 157—159°.

(*b*) Sulphuric acid (2 drops) was added to 3 : 4-dibenzyloxy-1-nitrobenzene (1·0 g.) in acetic anhydride (3 c.c.) and after 30 minutes the pale green solution was decomposed with water (25 c.c.). The crude product (0·7 g.) gave a clear melt at 91°, and was separated by fractional crystallisation into the monoacetate, m. p. and mixed m. p. 103—105°, and a little unchanged starting material.

(*c*) Sulphuric acid (1 drop) was added to 4 : 5-dibenzyloxy-2-nitrotoluene (0·5 g.) in acetic anhydride (1·5 c.c.) and after 30 minutes the brown mixture was worked up as above. The crude product (0·33 g.), m. p. 110°, was separated by fractional crystallisation from benzene–light petroleum into a major fraction of colourless needles, m. p. 133°, identical with the monoacetate monobenzyl ether obtained by using perchloric acid, and a small amount of unchanged starting material.

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KING'S COLLEGE OF HOUSEHOLD AND SOCIAL SCIENCE
(UNIVERSITY OF LONDON), W.8.

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112. *Acylation Reactions catalysed by Strong Acids. Part IV. "Benzoyl and Substituted Benzoyl Perchlorates" as C-Aroylating Agents.*

By H. BURTON and P. F. G. PRAILL.

"Benzoyl perchlorate," prepared *in situ* from silver perchlorate and benzoyl chloride, is an effective benzoylating agent and will convert anisole in nitromethane into *p*-methoxybenzophenone in at least 84% yield. Adding benzoic anhydride to the mixture markedly increases the yield of the ketone. A comparison is made of the yields of analogous ketones from three substituted "benzoyl perchlorates;" certain structural features of the substituted benzoyl cations are discussed.

Evidence for the adsorption of aroyl cations on silver chloride is discussed.

Note on Nomenclature.—The proposal (*J.*, 1950, 1203) to use the name acetylium for the acetyl cation (Ac^+) has been extended—with some reserve—to the designation of aroyl cations ($ArCO^+$) as aroylium (*e.g.*, benzoylium; *p*-nitrobenzoylium) (cf. *J.*, 1950, 2997).

IN Part II (*J.*, 1950, 2034) we investigated in some detail the action of acetylium perchlorate on anisole both in the absence and presence of an inert solvent, and also of acetic acid and

acetic anhydride. We expressed the view that acetylium perchlorate reacted as if it were the ion pair ($Ac^+ClO_4^-$) but we do realise that the evidence presented did not preclude the possibilities that the molecule was (*a*) ionically dissociated, (*b*) largely ionised, or (*c*) very easily ionising. We considered that our postulation, namely (*b*), did represent a reasonable working hypothesis which appeared to be fully substantiated by our experimental results. The increase in yield of ketone obtained by carrying out the reaction in a medium of increased dielectric constant was consistent with the view that the *rate* of the reaction

$$PhOMe + Ac^+ \longrightarrow OMe{\cdot}C_6H_4{\cdot}COMe + H^+$$

was affected (increased) and this appeared to us to be the only logical conclusion, since an *equilibrium* could not possibly be involved in this irreversible change. The only possibility of an equilibrium in the work discussed (*loc. cit.*) was in the reaction producing the acetylium perchlorate, *viz.*:

$$AgClO_4 + AcCl \rightleftharpoons AcClO_4 + AgCl$$

Although we did not make specific reference to this point we were sure from our results that the equilibrium in this reaction did lie entirely to the right; we have since confirmed this to some extent by showing that the yield of silver chloride was almost quantitative. We do however in the light of our further experience make this statement with some reserve and we discuss our reasons for this reservation on p. 531.

We assumed from our results with acetylium perchlorate that benzoylium perchlorate (" benzoyl perchlorate ") should be capable of preparation from silver perchlorate and benzoyl chloride and should be an effective benzoylating agent. We did not study its action on hydroxy-compounds but investigated its properties as a benzoylating agent towards anisole both in the absence and in the presence of nitromethane as a solvent of relatively high dielectric constant. Under these different conditions we were able to isolate at least 0·68 and 0·84 mol. respectively of *p*-methoxybenzophenone by using 1 mol. of benzoylium perchlorate with 4 mols. of anisole, and it is interesting to note that under comparable conditions exactly the same yields of *p*-methoxyacetophenone were obtained (*loc. cit.*) when using acetylium perchlorate. The results showed clearly that the reaction

$$PhOMe + Bz^+ \longrightarrow OMe{\cdot}C_6H_4{\cdot}COPh + H^+$$

was taking place and we surmised that the liberated hydrogen ion would react with benzoic anhydride, if present in the reaction mixture, to regenerate benzoylium ions:

$$H^+ + Bz_2O \rightleftharpoons Bz_2OH^+ \rightleftharpoons Bz^+ + BzOH.$$

When the reaction between benzoylium perchlorate (1 mol.) and anisole (4 mols.) was carried out in the presence of benzoic anhydride (3 mols.) again in nitromethane as a solvent, the yield of isolable ketone was increased to 1·32 mols. and thus exceeded that stoicheiometrically possible from the benzoylium perchlorate used. The increase in the yield of ketone was not so marked as in the case of the acetylium perchlorate–acetic anhydride experiments (*loc. cit.*) but we ascribe this to the probable greater reactivity of acetic anhydride towards hydrogen ions. We think that this follows from the known fact that acetic anhydride is more readily hydrolysed by aqueous acid than is benzoic anhydride. In this connexion however we should like to make it quite clear that we do not believe that the acetylium (or benzoylium) ion has any separate existence in an aqueous medium. We did refer to this point in Part I (*J.*, 1950, 1203) but we should like to draw particular attention to our view since it is apparent from some of the newer textbooks discussing reaction mechanisms that a misleading representation of this (and similar) acid-catalysed hydrolysis is being advanced. Our view is that the reaction proceeds as follows:

$$Ac_2O + H_3O^+ \rightleftharpoons Ac_2O^+H + H_2O \longrightarrow 2AcOH + H^+$$

We have also shown that, when sufficient benzoic anhydride was treated with 72% perchloric acid (1 mol.) in nitromethane (which was necessary to give a homogeneous mixture) in the presence of anisole (4 mols.), so that the resulting solution contained benzoic acid (4·4 mols.) and benzoic anhydride (4 mols.), there was a fairly rapid production of at least 1·08 mols. of *p*-methoxybenzophenone. The reaction did not occur as readily as the corresponding one with acetic anhydride and perchloric acid (Part I, *loc. cit.*) and again indicated the lower reactivity of benzoic anhydride.

We should point out that the yields of *p*-methoxybenzophenone quoted in the experiments involving the use of benzoic anhydride are strictly *minimal* since we had, of necessity, to adopt an alkaline hydrolysis to remove unchanged anhydride. We showed that the ketone was not cleaved by aqueous-alcoholic potassium hydroxide but the necessity of submitting the reaction product to this treatment must have involved some loss in the isolation processs.

Our proof that benzoic anhydride and hydrogen ion react in the manner we have indicated has also been confirmed recently by Gillespie (*J.*, 1950, 2997) who showed, by a cryoscopic method, that in an excess of sulphuric acid as the solvent, benzoic anhydride reacts thus:

$$Bz_2O + 2H_2SO_4 \longrightarrow Bz^+ + BzOH_2^+ + 2HSO_4^-$$

Gillespie's results are in a sense complementary to those of Treffers and Hammett (*J. Amer. Chem. Soc.*, 1937, **59**, 1708) who proved by a similar method that benzoic acid and 2 : 4 : 6-trimethylbenzoic acid behave differently in sulphuric acid. The former adds a proton to give the benzoic acidium ion, $BzOH_2^+$, whereas the latter affords the 2 : 4 : 6-trimethylbenzoylium ion, $C_6H_2Me_3{\cdot}CO^+$.

It was clearly of interest to study the reaction between " 2 : 4 : 6-trimethylbenzoyl perchlorate " and anisole. We found as expected that the addition of 2 : 4 : 6-trimethylbenzoyl chloride (1 mol.) to silver perchlorate (1 mol.) in anisole (4 mols.) and nitromethane resulted in the production of at least 0·92 mol. of 4-methoxy-2′ : 4′ : 6′-trimethylbenzophenone when the reaction was carried out at 0—5° for 45 minutes. This result appeared to us to be capable of interpretation in two ways, namely, (i) that the 2 : 4 : 6-trimethylbenzoylium ion was more reactive, that is, reacted faster, than the benzoylium ion, or (ii) that in the reaction

$$ArCOCl + AgClO_4 \rightleftharpoons ArCO^+ClO_4^- + AgCl$$

the equilibrium lies more to the right for the 2 : 4 : 6-trimethylbenzoyl than for the benzoyl compound. It will be apparent that the combined electron-repelling effects of the three methyl groups in the acid chloride would tend to help the separation of the chlorine in the sense $Me_3C_6H_2 \rightarrow CO \rightarrow Cl$, but we should also expect that once the cation had been formed, the same electronic effects would tend to neutralise the positive charge, *i.e.*, $Me_3C_6H_2 \rightarrow CO^+$. We found in these experiments that the yield of silver chloride was almost quantitative in both cases and we feel justified for this reason in assuming that (i) is the correct premise. It should be emphasised however that a final decision regarding reactivities cannot be made on the basis of yields alone.

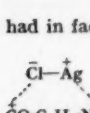
This point appeared to be capable of further verification by studying the preparation and the action of " *p*-anisoyl perchlorate " on anisole, since the powerful electron-repelling effect of the methoxyl group should be comparable with the combined effects of the methyl groups discussed above. We realised that in the case of the 2 : 4 : 6-trimethylbenzoyl compound there might be present a steric hindrance factor which is completely lacking in the *p*-anisoyl derivative. With the same molecular ratio of reactants under comparable conditions we were able to isolate also 0·92 mol. of 4 : 4′-dimethoxybenzophenone and an almost quantitative yield of silver chloride. We thus find that the *p*-anisoylium ion, $p\text{-}MeO{\cdot}C_6H_4{\cdot}CO^+$, in which the positive charge must to some extent again be neutralised by the electronic displacement of the methoxyl group, is as reactive as the 2 : 4 : 6-trimethylbenzoylium ion. It appears clear that a steric hindrance factor is not involved in the type of reaction we are investigating. In this sense the preparative value of such reactions might be of considerable value.

It appeared to us to be of considerable interest to study the preparation and reactivity of a cation in which the substituent in the benzene ring was of the opposite type to methoxyl and for this purpose we selected the *p*-nitrobenzoyl cation, $p\text{-}NO_2{\cdot}C_6H_4{\cdot}CO^+$. In this case the electron-attracting nitro-group should clearly tend to retard the removal of the chlorine but should also stabilise the cation once it is formed. Consequently, we should have expected this cation to be the most reactive of those studied. When the reaction between " *p*-nitrobenzoyl perchlorate " and anisole was carried out under otherwise identical conditions we found that the yield of 4-methoxy-4′-nitrobenzophenone was only 0·70 mol. An increase in the reaction time from 45 minutes to 2 hours did not affect the yield and it was thus apparent that the reaction stopped for a reason which may not, at first sight, be apparent. In both these sets of reaction conditions the weight of the supposed silver chloride produced actually exceeded the theoretical amount and it was obvious that some adsorption of either unchanged *p*-nitrobenzoyl chloride or the actual *p*-nitrobenzoylium ion was taking place. In our experimental procedure we had always washed the filtered silver chloride with an organic solvent and finally, as a

measure of safety, with water. We should have expected any adsorbed *p*-nitrobenzoyl chloride to have been largely removed by this procedure. Extraction of the supposed silver chloride with boiling alcohol removed an appreciable amount of *p*-nitrobenzoic acid leaving a residue of silver chloride which amounted to 95—100% of the theoretical amount. These results show definitely that the reaction

$$NO_2{\cdot}C_6H_4{\cdot}COCl + AgClO_4 \longrightarrow NO_2{\cdot}CH_4{\cdot}CO^+ClO_4^- + AgCl$$

had in fact gone to completion since adsorption of any of the acid chloride on silver chloride would have resulted in the non-reaction of an appreciable amount of silver perchlorate, which would therefore have remained in solution. Under these conditions the yield of silver chloride could not possibly have reached the value of 95—100%. We are of the opinion that in this case, the nitro-group with its lone pairs of electrons on the oxygen atoms is acting as an electron-donor to the silver cations but we do not wish to exclude the possibility that the chloride ion is acting similarly towards the organic cation (see *A* *). It is possible, and indeed probable, that in the case of the benzoylium cation the latter type of adsorption also occurs to a limited extent, but that the resulting complex is much less stable than that produced from the *p*-nitrobenzoylium ion. In our method of treatment of the silver chloride, the washing with water would clearly result in its reaction with the adsorbed cation to give *p*-nitrobenzoic acid and hydroxonium ion :



(*A*.)

$$NO_2{\cdot}C_6H_4{\cdot}CO^+ + 2H_2O \longrightarrow NO_2{\cdot}C_6H_4{\cdot}CO_2H + H_3O^+$$

Our findings appear to accord with this view.

The idea that an organic ion is capable of adsorption by a silver halide is not altogether novel. It has been postulated by Hughes, Ingold, *et al.* (*J.*, 1937, 1237, 1243) that a silver halide will adsorb an organic halide owing to a certain degree of electronic bonding between the silver cations and the (organic) halogen thus facilitating the separation of the organic radical as a cation. This view is not strictly comparable with our postulate but we feel that the two processes are closely allied.

If our view that the nitro-group is involved in an adsorption process is correct, then it would follow that an ion containing two nitro-groups might show, irrespective of its structure, an enhanced effect. It was noteworthy that when 3 : 5-dinitrobenzoyl chloride was added to a solution of silver perchlorate and anisole in nitromethane there was the obvious separation (after a short induction period) of silver chloride, but after 45 minutes at 0—5° there was no ketone in the reaction mixture. When the reaction mixture was kept for 2 hours we found that there was an uncontrollable and sudden rise in temperature from 0—5° to 75°, and we are of the opinion that the 3 : 5-dinitrobenzoylium ion had been largely adsorbed on the silver chloride and that, after a fairly long induction period, an extremely rapid reaction had occurred on the silver chloride surface. Extensive decomposition of any material formed during the reaction occurred, and we did not think it advisable to pursue this aspect of the investigation.

We had always been aware of the possibility that silver chloride might interfere in some way with the reaction of the " acyl perchlorate " prepared by the silver perchlorate technique, but we drew special attention in Part II (*loc. cit.*) to the fact that the results with acetylium perchlorate were the same irrespective of the method of its preparation. In this case the adsorption process may occur but is clearly of little consequence.

We also envisaged the possibility that the *p*-nitrobenzoylium (or similar) ion might react with the ethereal oxygen of anisole in the way we have discussed in Part III (preceding paper), thus leading to, for example, some phenyl *p*-nitrobenzoate :

$$PhOMe + NO_2{\cdot}C_6H_4{\cdot}CO^+ \rightleftharpoons NO_2{\cdot}C_6H_4{\cdot}CO{\cdot}O^+PhMe \longrightarrow NO_2{\cdot}C_6H_4{\cdot}CO_2Ph + Me^+$$

We made a careful search for the presence of this ester in our reaction product but without success. We did find however that repeated fractionation gave a few crystals of a substance which was ketonic and was most probably 2-methoxy-4′-nitrobenzophenone.

Experimental.

Materials.—Benzoyl chloride was an AnalaR reagent. 2 : 4 : 6-Trimethylbenzoyl chloride was prepared by Barnes's method (*Org. Synth.*, 1941, **21**, 77). Commercial *p*-nitrobenzoyl chloride was treated with thionyl chloride and subsequently purified by repeated crystallisation from carbon tetrachloride. Commercial *p*-anisoyl chloride was purified by treatment with thionyl chloride and subsequent

* Scheme (*A*) is not intended to be anything other than illustrative.

repeated vacuum-distillation. " Pure " 3 : 5-dinitrobenzoyl chloride (see Introduction) was crystallised first from carbon tetrachloride and then from a large volume of light petroleum (b. p. 40—60°) in which it was only sparingly soluble. Benzoic anhydride, m. p. 42°, was dried for at least 48 hours over phosphoric oxide. Anisole and nitromethane were dried and redistilled. Silver perchlorate was treated as in Part II (*loc. cit.*).

p-*Methoxybenzophenone.*—(*a*) Silver perchlorate (0·05 g.-mol.), dissolved in anisole (0·2 g.-mol.) and nitromethane (43·2 g.), was cooled to 0° and benzoyl chloride (0·05 g.-mol.) was added during 15—18 minutes, the temperature being kept at 0—5°. The initially yellow mixture slowly became more brown on being kept at 0—5° for 45 minutes. The mixture was poured on crushed ice (*ca.* 150 g.) and, after all the ice had melted, the silver chloride was filtered off and washed with water and with ether. The oily material in the filtrate was extracted twice with ether and the combined ethereal extracts were washed successively with water, 2N-sodium hydroxide (twice), and water (twice). The dried (Na_2SO_4) ethereal solution was evaporated and the residue fractionated; the fraction, b. p. 180—190°/7—8 mm., solidified on cooling (0·042 g.-mol.) and had m. p. 58°. It crystallised from light petroleum (b. p. 40—60°) in clusters of colourless needles, m. p. 61—62° (Found : C, 79·2; H, 5·6. Calc. for $C_{14}H_{12}O_2$: C, 79·2; H, 5·7%). The ketone was further characterised as the 2 : 4-*dinitrophenylhydrazone*, bright red needles (from ethyl acetate), m. p. 221—222° (Found : C, 61·2; H, 4·0. $C_{20}H_{14}O_5N_4$ requires C, 61·2; H, 4·1%). Preparation of this and other 2 : 4-dinitrophenylhydrazones of the substituted benzophenones required heat.

When the reaction mixture obtained as under (*a*) was kept for 2 hours the yield of ketone was unchanged.

In the absence of nitromethane the yield of ketone was 0·034 g.-mol.

(*b*) A solution of silver perchlorate (0·05 g.-mol.) and benzoic anhydride (0·15 g.-mol.) in anisole (0·2 g.-mol.) and nitromethane (111 g.) was cooled to 0°, and benzoyl chloride (0·05 g.-mol.) added during 15 minutes at 0—5°. After being kept for 45 minutes at 0—5° the deep-orange mixture was poured on crushed ice (*ca.* 200 g.). The silver chloride was filtered off and washed repeatedly with ether, and the oily product extracted with ether. The ethereal solution was washed with water and then evaporated, the last stage being carried out under reduced pressure. The solid residue was dissolved in 96% alcohol (70 c.c.), and a solution of potassium hydroxide (17·5 g.) in water (15 c.c.) added cautiously. The mixture was then refluxed for 1 hour, as much of the alcohol as possible was distilled off, and the residue diluted with water and re-extracted with ether. The ethereal extract was treated as previously. The yield of *p*-methoxybenzophenone was 0·066 g.-mol., and the m. p. 58—60° before recrystallisation.

(*c*) Benzoic anhydride (0·155 g.-mol.) was dissolved in a mixture of nitromethane (114·5 g.) and anisole (0·1 g.-mol.), and the solution was cooled to 0°. 72% Perchloric acid (3·5 g. = 0·025 g.-mol.) was cautiously added during 15—16 minutes. After addition of the first few drops of acid the mixture became bright yellow, solid material separated, and in spite of strong cooling the temperature rose to 10°. The mixture was cooled rapidly to 5° and then kept between 0° and 5° for the rest of the addition. After being kept at 0—5° for a further 45 minutes, the mixture was poured on crushed ice (150—200 g.), a reddish-violet colour being produced. The ketone (0·027 g.-mol.), m. p. 58—60°, was isolated as described under (*b*).

4-*Methoxy*-2′ : 4′ : 6′-*trimethylbenzophenone.*—(*a*) A solution of 2 : 4 : 6-trimethylbenzoyl chloride (mesitoyl chloride) (0·025 g.-mol.) in nitromethane (4·6 g.) was added during 15 minutes to a cooled (0—5°) solution of silver perchlorate (0·025 g.-mol.) in anisole (0·025 g.-mol.) and nitromethane (13·5 g.). The bright yellow mixture was kept at 0—5° for 45 minutes and then filtered. The solid was washed repeatedly with chloroform and finally with water. The filtrate which was collected directly on crushed ice became almost colourless. After extraction of the filtrate twice with chloroform, the combined extracts were washed twice with 2N-aqueous ammonia and then with water. Evaporation of the solution gave a residue of *ketone* which solidified on trituration with a little light petroleum (b. p. 60—80°) to colourless needles (0·023 g.-mol.). Crystallisation from alcohol gave colourless needles, m. p. 76—77° (Found : C, 79·2; H, 7·1. $C_{17}H_{18}O_2$ requires C, 80·3; H, 7·1%).

(*b*) A mixture of *p*-anisoyl chloride (0·05 g.-mol.), mesitylene (0·05 g.-mol.), 95% zinc chloride (0·028 g.-mol.), and nitromethane (14·5 g.) was refluxed (*ca.* 3½ hours) until all the zinc chloride had dissolved. The crude ketone (0·03 g.-mol.) obtained by pouring the mixture on crushed ice, extracting the product with ether, and washing the ethereal extract with 2N-sodium hydroxide and water crystallised from alcohol in colourless needles, m. p. and mixed m. p. 76—77°.

The ketone did not give a 2 : 4-dinitrophenylhydrazone.

A solution of the ketone in an excess of concentrated sulphuric acid was heated on the steam-bath for 1—2 minutes. The intense yellow colour which developed disappeared on treatment of the solution with cold water, and the oily droplets then slowly crystallised. The solid melted almost completely at 75—76° but the melt did not become absolutely clear until 125—130°. A mixed m. p. with the original ketone was also 75—76° but a faint opalescence persisted until a little above 80°. When the crude product was shaken with dilute sodium hydrogen carbonate solution, the filtered solution gave on acidification a trace of solid material which redissolved on the addition of alkali.

4 : 4′-*Dimethoxybenzophenone.*—*p*-Anisoyl chloride (0·05 g.-mol.) in nitromethane (4·2 g.) was added during 15 minutes to a solution of silver perchlorate (0·05 g.-mol.) in nitromethane (27·0 g.) and anisole (0·05 g.-mol.) at 0—5°. After a further 45 minutes at 0—5° the silver chloride was filtered off from the yellow-brown mixture and the filtrate collected directly on crushed ice (*ca.* 150 g.). The silver chloride was washed repeatedly with chloroform which was then used to extract the aqueous phase. The combined extracts were washed thrice with 2N-sodium hydroxide and then with water. The residue from the evaporated extract solidified to a crystalline mass which after being washed with light petroleum (b. p. 40—60°) had m. p. 140° (yield, 0·046 g.-mol.). The ketone crystallised from alcohol in colourless

needles (or flakes), m. p. 143° (Found: C, 75·0; H, 5·8. Calc. for $C_{15}H_{14}O_3$: C, 75·0; H, 5·8%). The ketone was further characterised as the 2 : 4-*dinitrophenylhydrazone*, bright red needles, m. p. 198°, from chloroform–alcohol (3 : 1) or from ethyl acetate (Found: C, 59·9; H, 4·1; N, 13·2. $C_{21}H_{18}O_6N_4$ requires C, 59·7; H, 4·3; N, 13·3%).

A similar experiment in which the reaction mixture was kept for 2 hours gave the same results.

A trace only of *p*-anisic acid was obtained by acidification of the alkaline extracts of the reaction product.

4-*Methoxy*-4′-*nitrobenzophenone*.—Silver perchlorate (0·05 g.-mol.) was dissolved in anisole (0·05 g.-mol.) and nitromethane (27·0 g.) and treated at 0° with a solution of *p*-nitrobenzoyl chloride (0·05 g.-mol.) in nitromethane (23·3 g.) during 15 minutes. The mixture was kept for 45 minutes at 0—5° and then filtered (sintered-glass filter), the filtrate being allowed to drop directly on crushed ice (*ca.* 150 g.). The solid was washed repeatedly with chloroform, until all the pink colour was removed. The bright red semi-solid mass which separated from the filtrate was extracted repeatedly with more chloroform, and the combined extracts were washed with 2N-aqueous ammonia until the washings no longer gave a precipitate on acidification with 2N-sulphuric acid. After being washed with water the chloroform extracts were dried and evaporated, the excess of nitromethane and anisole being removed in a vacuum. The solid residue, after being washed with a little ether, consisted of pale pink or yellow needles (0·035 g.-mol.) which crystallised from alcohol in almost colourless needles, m. p. 121° (Found: C, 66·0; H, 4·5; N, 5·2. Calc. for $C_{14}H_{11}O_4N$: C, 65·4; H, 4·3; N, 5·4%).

The ketone was characterised as its 2 : 4-*dinitrophenylhydrazone*, scarlet plates (from chloroform), m. p. 265° (decomp.) (Found: C, 54·8; H, 3·4; N, 15·6. $C_{20}H_{15}O_7N_5$ requires C, 54·9; H, 3·4; N, 16·0%).

Evaporation of the various mother-liquors from the crystallisations gave variable amounts of a solid which melted at about 93°. When this was fractionated from methanol two types of crystal were obtained: (*a*) fine needles, m. p. 121°, identical (m. p. and mixed m. p.) with the above ketone, and (*b*) a small amount of stout prisms, m. p. 117° (Found: C, 65·6; H, 4·3; N, 5·6. $C_{14}H_{11}O_4N$ requires C, 65·4; H, 4·3; N, 5·4%), which depressed the m. p. of the above ketone and of phenyl *p*-nitrobenzoate (m. p. 126°) and appeared to be (?) 2-*methoxy*-4′-*nitrobenzophenone*. The prisms gave a bright yellow 2 : 4-dinitrophenylhydrazone, m. p. 210° (decomp.), which from its nitrogen content (Found: N, 16·8%) appeared to be contaminated with a little 2 : 4-dinitrophenylhydrazine.

Extraction of the original filter containing the silver chloride with boiling 96% ethyl alcohol and subsequent evaporation of the extracts gave *p*-nitrobenzoic acid (1·2 g.), identified by m. p. and mixed m. p. The residual silver chloride amounted to 95—100% of the theoretical amount.

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KING'S COLLEGE OF HOUSEHOLD AND SOCIAL SCIENCE
(UNIVERSITY OF LONDON), W.8. [*Received, November 16th*, 1950.]

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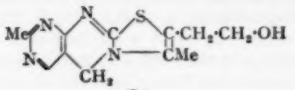
113. *Aneurin. Part X. The Mechanism of Thiochrome Formation from Aneurin and Aneurin Disulphide.*

By P. SYKES and A. R. TODD.

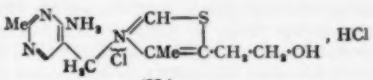
When aneurin disulphide is heated in various solvents it yields thiochrome and a colourless compound, m. p. 237° (cf. Zima and Williams, *Ber.*, 1940, **73**, 941). Evidence is presented for the view that this colourless substance is the thiazolone (IV), and an account is given of an extended series of experiments carried out in endeavours to synthesise (IV) by other routes. The thiazolone (IV) is not readily convertible into thiochrome. A mechanism is suggested to explain the production of thiochrome, together with (IV), from aneurin disulphide, and a new mechanism is advanced to account for the formation of thiochrome by oxidation of aneurin itself.

ALTHOUGH thiochrome (I) is readily formed by the oxidation of aneurin (vitamin B_1) (II) in alkaline solution with potassium ferricyanide (Barger, Bergel, and Todd, *Ber.*, 1935, **68**, 2257), its preparation in quantity by this route is inconvenient. The best preparative procedure rests on the observation of Zima and Williams (*Ber.*, 1940, **73**, 941) that aneurin disulphide (III) yields thiochrome (I), together with at least one colourless substance when heated in high-boiling solvents such as ethylene glycol. Some time ago we had occasion to prepare a substantial amount of thiochrome and we employed a method of this type in which a solution of aneurin disulphide in *iso*butanol is refluxed for two hours; we are indebted to Messrs. Hoffmann-La Roche & Co., Basle, for details of this method which had been used in their laboratories. Our results were similar to those of Zima and Williams (*loc. cit.*) in that

we obtained, in addition to thiochrome, substantial amounts of the colourless substance $C_{12}H_{16}O_2N_4S$, m. p. 237°, which these authors suggested might be the thiazolone derivative (IV) corresponding to aneurin, although they advanced no evidence to support their suggestion. The production of thiochrome from aneurin disulphide in this way is itself interesting, and if the colourless by-product is indeed (IV) then earlier views on the mechanism of thiochrome formation from aneurin (Barger, Bergel, and Todd, *loc. cit.*; Windaus, Tschesche, and Grewe, *Z. physiol. Chem.*, 1935, **237**, 98), in which (IV) is a postulated intermediate, would require revision. The present paper records some experiments designed to establish the validity of structure (IV) for the colourless product and to throw light on the mechanism by which thiochrome is produced from aneurin and aneurin disulphide.



(I.)



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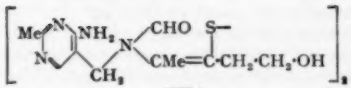

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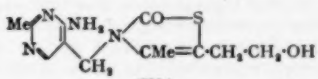
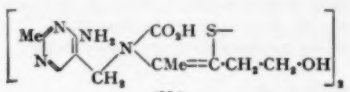
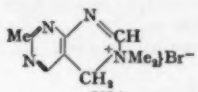


(IV.)

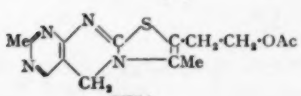
The decomposition of aneurin disulphide was examined in several solvents, but the yield of colourless substance, m. p. 237°—henceforth called, for convenience, " aneurin thiazolone "—was highest in *iso*butanol; thiochrome was formed simultaneously in every case. " Aneurin thiazolone," which is only very slightly soluble even in hot water, is a colourless, non-fluorescent, monoacid base which dissolves in dilute acid and is reprecipitated unchanged by addition of alkali in the cold. It is unaffected by treatment with sulphite under conditions which cause cleavage of aneurin, or by heating with aniline, benzylamine, or ammonia in alcoholic solution, and does not absorb hydrogen at room temperature in presence of a platinum catalyst; with acetic anhydride, it yields a monoacetyl derivative. When it is heated with dilute sodium hydroxide solution decomposition occurs with formation of sulphide, and similar treatment with hydrochloric acid yields 4-amino-5-aminomethyl-2-methylpyrimidine. After oxidation of a solution of " aneurin thiazolone " in one equivalent of dilute hydrochloric acid with hydrogen peroxide, two equivalents of alkali were required for neutralisation, and the oxidation product was isolated as its sodium salt. Acidification of a solution of this salt and then warming afforded carbon dioxide, and when the salt was heated with anhydrous formic acid decarboxylation occurred followed by formylation of the decarboxylation product, to give aneurin disulphide (III). On this evidence, the oxidation product is formulated as (V) and the " aneurin thiazolone " itself has almost certainly the originally postulated structure (IV). It is worthy of mention that, if the thiazolone is heated above its melting point for considerable periods, only negligible amounts of thiochrome (detected by its fluorescence) are produced.



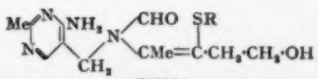
(V.)



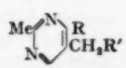
(VI.)



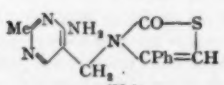
(VII.)



(VIII.)



(IX.)

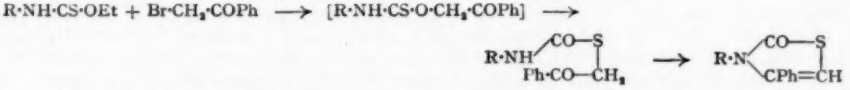


(X.)

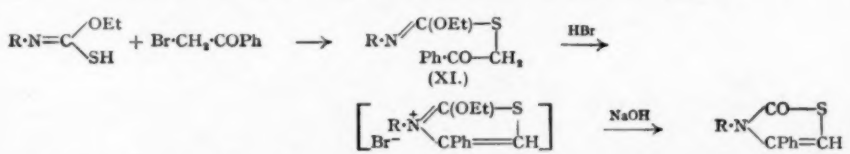
Although we were reasonably certain that the " aneurin thiazolone " had structure (IV), it was decided to attempt the synthesis of (IV) so as to set the matter beyond doubt. Many

possible methods were investigated, but none was successful. A number of features of chemical interest arose during these investigations, however. Initial attempts to condense 4-amino-5-bromomethyl-2-methylpyrimidine with 5-2′-acetoxyethyl-4-methylthiazol-2-one, either as such or as a metal derivative, were quite unsuccessful. When the two compounds were heated in butanol solution only 4-amino-5-butoxymethyl-2-methylpyrimidine (IX; R = NH_2, R′ = OBu^n) was obtained, while with dimethylformamide as a solvent a product was isolated which, on the evidence of analysis and general behaviour, is formulated as (VI). A more likely approach involved initial formation of a quaternary salt from 4-amino-5-bromomethyl-2-methylpyrimidine and 5-2′-acetoxyethyl-2-chloro-4-methylthiazole, but under the conditions employed quaternisation was followed by a spontaneous cyclisation yielding *O*-acetylthiochrome (VII). The compound (VIII; R = Na) which is the immediate precursor of aneurin disulphide in its production from aneurin, might form a suitable starting material for (IV) if the formyl group could be removed and the product caused to react with carbonyl chloride. Hydrolytic removal of this group in (VIII; R = Na) is impossible, since acid re-forms aneurin, and alkali causes elimination of sulphur as sulphide, and it was found, not unexpectedly, that the *S*-alkyl and *S*-aralkyl ethers (VIII; R = Me, $PhCH_2$, and p-$NO_2{\cdot}C_6H_4{\cdot}CH_2$) were hydrolysed at the sulphur linkage before any removal of the formyl group could be effected.

Attention was now turned to the method of Walther and Greifenhagen (*J. pr. Chem.*, 1907, [ii], **75**, 201), who synthesised various thiazol-2-ones by condensing arylthiourethanes with ω-bromoacetophenone. 4-Amino-2-methyl-5-thioncarbethoxyaminomethylpyrimidine (IX; R = NH_2, R′ = NH·CS·OEt) was prepared by reaction of *OS*-diethyl xanthate (Debus, *Annalen*, 1850, **75**, 121) with the corresponding 5-aminomethylpyrimidine. Heated in the form of its hydrochloride with ω-bromoacetophenone in dioxan, it gave a small yield of 3-(4-amino-2-methyl-5-pyrimidyl)methyl-4-phenylthiazol-2-one (X). This thiazolone, on prolonged heating above its melting point, gave a small amount of fluorescent material, just as did the "aneurin thiazolone." No trace of a thiazolone was obtained, however, in experiments in which the thiourethane (IX; R = NH_2, R′ = NH·CS·OEt) or its salts were treated under a varietv of conditions with 3-acetoxy-1-bromopropyl methyl ketone, or the corresponding chloro- and iodo-ketones, α-aceto-α-bromobutyrolactone, or bromoacetone. In each case, decomposition of the halogen compound occurred before condensation could take place. In the same way, the corresponding benzylthiourethane (IX; R = NH_2, R′ = NH·CS·O·CH_2Ph) failed to react with these aliphatic halogen compounds, although with ω-bromoacetophenone it yielded (X) more readily than did the ethylthiourethane. The mechanism proposed by Walther and Greifenhagen (*loc. cit.*) for the production of thiazolones by their method involved an initial elimination of alkyl halide and a subsequent migration of a group from oxygen to sulphur before cyclisation:



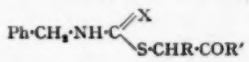
Migration of alkyl groups from oxygen to sulphur in simple thiocarbamates has been observed by Wheeler and Barnes (*Amer. Chem. J.*, 1899, **22**, 141), but we believe that, at least in the reactions we have studied, the following alternative mechanism plays a major rôle:

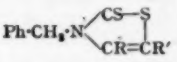


This belief rests on the fact that we were unable to detect any alkyl bromide during our reactions and bromide ion was always present in the resulting solutions. It is also significant that condensation of the thiourethane (IX; R = NH_2, R′ = NH·CS·OEt) with ω-bromoacetophenone occurs to a very small extent only unless the thiourethane is first converted into a salt or, better, the ethanol used as a solvent contains dissolved hydrogen chloride. Presumably, in the absence of additional acid, the hydrogen bromide liberated in the first stage of the reaction is used up in forming a salt of the intermediate pyrimidine derivative (XI) and

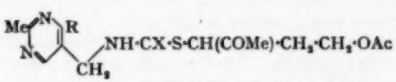
additional acid facilitates cyclisation. Intermediates of type (XI) in which the ethoxy-group is replaced by hydrogen or alkyl were isolated by Todd, Bergel, and Karimullah (*Ber.*, 1936, **69**, 217) as products of the reaction between *N*-substituted thioamides and α-halogeno-ketones and it was shown by these authors that their cyclisation to quaternary thiazolium salts occurred on heating their hydrochlorides, or, more rapidly by heating them in ethanol containing excess of anhydrous hydrogen chloride. When the pyrimidine thiourethane (IX; R = NH_2, R′ = NH·CS·OEt) was treated in ethanol with one equivalent of sodium ethoxide and then allowed to react with ω-bromoacetophenone, the intermediate (XI; R = 4-amino-2-methyl-5-pyrimidylmethyl) was obtained. This product was unaffected by refluxing ethanol, but heating it in ethanol containing dissolved hydrogen chloride converted it smoothly into the thiazolone (X); the same intermediate was also found in small amount in the mother-liquors from experiments in which the free thiourethane had been condensed with ω-bromoacetophenone in the absence of acid.

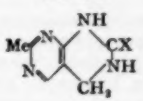
Although we considered that the thiazolone synthesis followed the route above indicated, it seemed possible that a compound of type (XII) postulated as an intermediate by Walther and Greifenhagen (*loc. cit.*) might be cyclised to give a thiazolone, and some model experiments were carried out to test this. Phenacyl *N*-benzylthiolcarbamate (XII; X = O, R = H, R′ = Ph), however, could not be dehydrated to yield a thiazolone. More success attended the use of dithiocarbamates. Phenacyl (XII; X = S, R = H, R′ = Ph) and 3-acetoxy-1-acetylpropyl *N*-benzyldithiocarbamate (XII; X = S, R = CH_2·CH_2·OAc, R′ = Me) were prepared; when these were heated above their melting points, gas was evolved and they were converted smoothly into 3-benzyl-4-phenylthiazol-2-thione (XIII; R = Ph, R′ = H) and 5-2′-acetoxyethyl-3-benzyl-4-methylthiazol-2-thione (XIII; R = Me, R′ = CH_2·CH_2·OAc) respectively. When an attempt was made to prepare a thiazol-2-thione in similar fashion from 3-acetoxy-1-acetylpropyl *N*-(4-amino-2-methyl-5-pyrimidyl)methyldithiocarbamate (XIV; R = NH_2, X = S), however, a cyclisation, involving the 4-amino-group on the pyrimidine nucleus, occurred, yielding 1 : 2 : 3 : 4-tetrahydro-7-methyl-2-thio-1 : 3 : 6 : 8-tetra-azanaphthalene (XV; X = S), a compound already described by Bergel and Todd (*J.*, 1938, 26; there called 2-thio-7-methyl-1 : 2 : 3 : 4-tetrahydro-1 : 3 : 6 : 8-benztetrazine). The corresponding monothiocarbamate (XIV; R = NH_2, X = O) was also prepared, but it cyclised in an analogous manner when heated to give (XV; X = O), which was identified by comparison with a specimen synthesised by heating the reaction product of 4-amino-5-aminomethyl-2-methylpyrimidine hydrochloride with potassium cyanate to 280° until ammonia evolution ceased. The ease with which these cyclisations occur is surprising in view of the difficulty encountered by Bergel and Todd (*loc. cit.*) in preparing (XV; X = S) by a not dissimilar method. One possible method of avoiding this unwelcome type of ring-closure would be to utilise 5-aminomethyl-4-chloro-2-methylpyrimidine as starting material for the thiocarbamate intermediate

(XII.) 

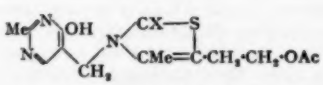


(XIII.)

(XIV.) 



(XV.)

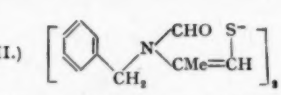
(XVI.) 

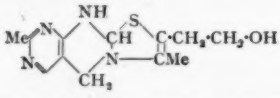
and to replace the chlorine atom in the final product by an amino-group. Unfortunately, however, we were unable to prepare this chloro-compound although various methods were tried. A second less attractive possibility was to start from 5-aminomethyl-4-hydroxy-2-methylpyrimidine and replace the 4-hydroxy-group in the final product by an amino-group. From this amine, the appropriate di- and mono-thiocarbamates (XIV; R = OH, X = S and O) were prepared and these, when heated, yielded 5-2′-acetoxyethyl-3-(4-hydroxy-2-methyl-5-pyrimidyl)methyl-4-methylthiazol-2-thione (XVI; X = S) and 5-2′-acetoxyethyl-3-(4-hydroxy-2-methyl-5-pyrimidyl)methyl-4-methylthiazol-2-one (XVI; X = O) respectively. Attempts to replace the hydroxy-group in either of these compound by chlorine caused gross decomposition.

The thiazolone (XVI; X = O) differs from the acetyl derivative of the " aneurin thiazolone " (IV) only in that the pyrimidine ring bears a hydroxy- rather than an amino-group in position 4, and it seemed possible that it might be obtainable from (IV). Cerecedo and Soodak (*J. Amer. Chem. Soc.*, 1944, **66**, 1988) describe a deamination procedure for the conversion of aneurin into its 4-hydroxy-analogue; we were unable to confirm the observations of these workers on aneurin itself and the method effected no deamination when applied to the " aneurin thiazolone," although the thiazolone ring was opened.

Assuming that structure (IV) correctly represents the " aneurin thiazolone," it is of interest to consider the manner in which it is produced together with thiochrome from aneurin disulphide. The reaction is carried out by simple heating in a variety of solvents and, although *iso*butanol appears to give the best results, *n*-butanol, ethylene glycol, glycerol, pyridine, and even water are all satisfactory. Although, as already mentioned, prolonged heating above its melting point converts a small amount of the thiazolone into thiochrome, there is no evidence that the two are interconvertible under the conditions used in their formation from aneurin disulphide; each of them is unaffected by prolonged refluxing in *iso*butanol. It seems very likely that thiochrome and the thiazolone are produced more or less simultaneously from one aneurin disulphide molecule, and the fact that they are not isolated in equimolecular proportions after the reaction is doubless due to its being much more difficult to isolate thiochrome than thiazolone. Some support for this view is found in the fact that the simple model disulphide (XVII) can be recovered unchanged after prolonged refluxing in various solvents. Although it could not yield a thiochrome analogue it could, in theory, yield a thiazolone analogous to (IV). It may well be that, before fission of a disulphide of this type will proceed, the possibility of forming a thiochrome-like compound must exist, *i.e.*, that the amino-group(s) in aneurin disulphide play an essential part in the fission.

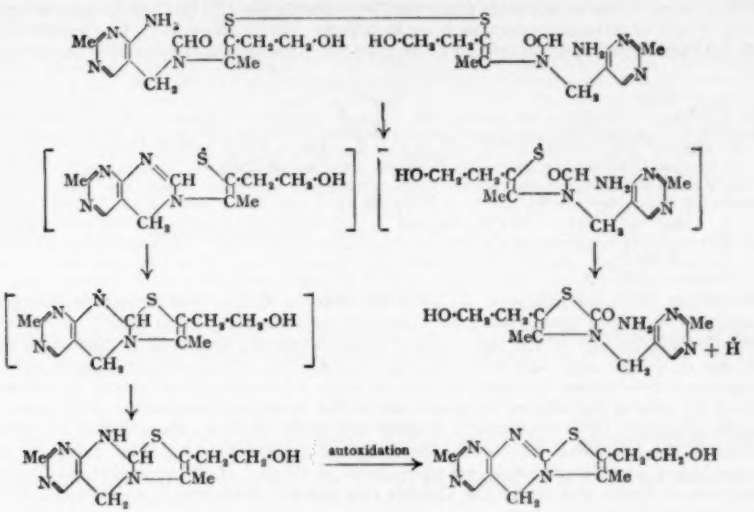
Evidence regarding the mechanism by which thiochrome is produced from aneurin disulphide was obtained by refluxing the latter in *iso*butanol in a nitrogen atmosphere, the solvent having been previously freed from air by boiling it for some time while a stream of air-free nitrogen was passed through it. When the solution was allowed to cool in the absence of air, the thiazolone (IV) crystallised, but at no stage was there any trace of the brilliant blue fluorescence of thiochrome. When, however, air was admitted to the apparatus at the end of the experiment, with the solution either cold or hot, an intense blue fluorescence appeared almost immediately and thiochrome could subsequently be isolated. From these results it appears highly likely that dihydrothiochrome (XVIII) is the immediate precursor of thiochrome in the normal aneurin disulphide fission. Dihydrothiochrome, which is formed by sodium dithionite reduction of thiochrome (Kuhn, Wagner-Jauregg, van Klaveren, and Vetter, *Z. physiol. Chem.*, 1935, **234**, 196), is known to be oxidised spontaneously in air.

(XVII.) 

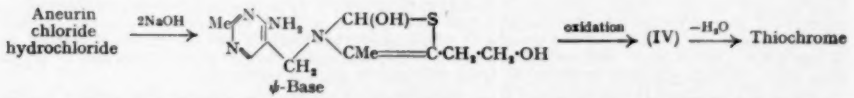
 (XVIII.)

On the available evidence, it is tentatively suggested that when aneurin disulphide is heated in solvents there is initially a cyclisation by loss of water between one of the formyl groups and the adjacent 4-amino-group on a pyrimidine nucleus, followed by a fission of the molecule at the disulphide linkage to yield two thiol radicals. In the radical containing the cyclised fragment, intramolecular addition across the C=N system occurs, yielding the dihydrothiochrome radical which is converted into dihydrothiochrome by exchange with solvent, and then undergoes spontaneous oxidation to thiochrome itself in presence of air. The other radical produced in the initial fission yields the " aneurin thiazolone " (IV) by reaction of the thio-radical with the formyl group and elimination of a hydrogen radical. The proposed scheme is indicated on p. 539.

The initial dehydration postulated in the scheme presents no obstacle, since it seems likely that those derivatives of aneurin supposedly containing a free formyl group exist partly in such a cyclic form (Zima and Williams, *loc. cit.*). The addition of free radicals to unsaturated systems is well known, although those hitherto described involve the C=C rather than the C=N system (cf. Waters, " Chemistry of Free Radicals," Oxford, 1946, p. 188). When pyridine is used as a solvent, the radical-terminating action could be exerted by the water produced in the initial dehydration, if not by the pyridine itself; it is perhaps worthy of mention in this connection that the reaction is slower in pyridine than in other solvents, as judged by the development of fluorescence and by the amounts of the thiazolone isolated after varying periods of reaction.



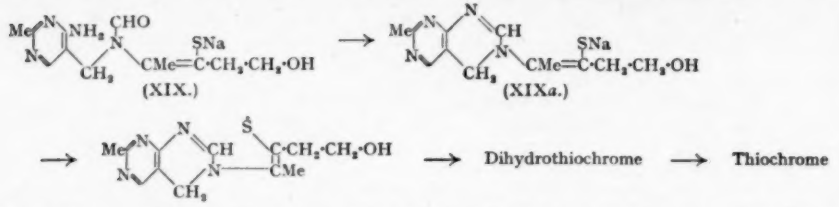
The mechanism originally postulated for the conversion of aneurin into thiochrome was oxidation of the aneurin ψ-base to the thiazolone (IV), followed by cyclisation (Barger, Bergel, and Todd, *loc. cit.*) :



This mechanism seemed satisfactory at the time, the more so as much the best reagent for bringing about the conversion was alkaline potassium ferricyanide, which is known to effect the change ψ-base ⟶ pyridone in the analogous pyridinium compounds. Porphyrexide (Kuhn and Vetter, *Ber.*, **1935**, **68**, 2375) can also be used to prepare thiochrome but most other oxidising agents, *e.g.*, iodine, hydrogen peroxide, produce mainly aneurin disulphide from aneurin. On the evidence presented in this paper, in particular the observation that conversion of the thiazolone (IV) into thiochrome is very small even above 250°, it is clear that the mechanism of Barger, Bergel, and Todd (*loc. cit.*) cannot be correct. A modified mechanism which was favoured by Kuhn and Vetter (*loc. cit.*) postulated cyclisation at the ψ-base stage, followed by oxidation of the dihydrothiochrome (XVIII). A strong objection to this view is found in the fact that the oxidation of dihydrothiochrome to thiochrome proceeds spontaneously in air, so that no ferricyanide or other oxidising agent would be required. All attempts to demonstrate the existence of the aneurin ψ-base by oxidising aneurin in the presence of two equivalents of alkali under conditions most favourable to thiazolone formation failed, no trace of (IV) being obtained. It may well be that the ψ-base does not exist as such in alkaline solution and that aneurin exhibits an extreme case of the phenomenon observed in benzthiazole derivatives by Mills, Clark, and Aeschlimann (*J.*, **1923**, **123**, 2353), where addition of one equivalent of alkali to the quaternary chloride converted half of it directly into the sodium salt of the thiol produced by opening the thiazole ring, while the other half of the chloride remained unchanged; in these experiments no ψ-base could be isolated.

We consider that the peculiar virtue of ferricyanide as an oxidising agent in converting aneurin into thiochrome lies in its being a one-electron oxidising agent which oxidises the sodium salt of the cyclised thiol-form of aneurin to the free radical; ferric salts are particularly suitable for this type of oxidation (cf. Waters, *op. cit.*, p. 283). Some of the cyclised form (XIX*a*) will always be present in alkaline solutions of the simple thiol salt (XIX) (Zima and Williams, *loc. cit.*). Formation of thiochrome from the thiol radical is believed to proceed in the manner postulated in our discussion of its formation from aneurin disulphide.

Doubtless, some of the ferricyanide takes part in oxidising the dihydrothiochrome intermediate, but this is not an essential function if air is present. It is noteworthy that mercuric oxide, which has been shown to be an effective substitute for potassium ferricyanide in the preparation



of thiochrome (Holman, *Biochem. J.*, 1944, **38**, 388), is also a one-electron oxidising agent. Two-electron oxidising agents such as hydrogen peroxide and iodine would be expected to convert the sodium salt of the thiol form of aneurin directly into aneurin disulphide without production of thiochrome; this is in fact what is observed. Some support for this view of the mechanism of thiochrome formation (which is indicated schematically above) is provided by the effect of varying the amount of alkali used in the ferricyanide oxidation of aneurin. If to a sample of aneurin three equivalents of alkali are added, followed immediately by potassium ferricyanide, the amount of thiochrome (estimated fluorimetrically) produced is greater than in a corresponding experiment using two equivalents of alkali. If the oxidation mechanism did not involve an initial opening of the thiazole ring system, there would have been little or no difference between the two.

Experimental.

Conversion of Aneurin Disulphide into Thiochrome (I) *and "Aneurin Thiazolone"* (IV).—Aneurin disulphide (III) (2 g.) was refluxed for 2 hours in *iso*butanol (40 c.c.), and the highly fluorescent solution then allowed to cool. Colourless needles of aneurin thiazolone (IV) [3-(4-amino-2-methyl-5-pyrimidyl)-methyl-5-2′-hydroxyethyl-4-methylthiazol-2-one] (0·47 g.), m. p. 237°, separated. From the mother-liquors, thiochrome (I) (0·14 g.) was obtained. (This follows the method used by Messrs. Hoffmann-La Roche & Co., Ltd., Basle.) Rather less conversion took place when ethylene glycol (Zima and Williams, *Ber.*, 1940, **73**, 941), glycerol, pyridine, or water was used in place of *iso*butanol.

When the experiment was repeated in an atmosphere of oxygen-free nitrogen (the solvent having previously been boiled out in a nitrogen stream), no fluorescence was observed until air was admitted to the apparatus, whereupon the characteristic colour due to thiochrome was seen at once. The yields of thiochrome and thiazolone obtained were almost exactly the same as when the conversion was carried out in the presence of air.

The thiazolone gave a negative result in the formaldehyde–azo-test (Kinnersley and Peters, *Biochem. J.*, 1934, **28**, 667). Heated to 280° for some time, the substance darkened and charred and then showed faintly the yellow-green fluorescence in the solid and blue fluorescence in butanol solution, characteristic of thiochrome.

Acetylation of "Aneurin Thiazolone."—A solution of the thiazolone (IV) (0·94 g.) in acetic anhydride (18 c.c.) was treated with pyridine (0·5 c.c.) and kept at room temperature for 48 hours, diluted with ethanol (50 c.c.), and then evaporated under reduced pressure. The residual gum was dissolved in a little water, made neutral with N-sodium hydroxide, and evaporated to dryness under reduced pressure, and the residue extracted with hot chloroform. The gum obtained by evaporating the chloroform extract crystallised from acetone, giving short colourless needles of the *acetyl* derivative (0·63 g., 58%), m. p. 174° (Found: C, 52·5; H, 5·6; N, 16·9%; *M*, 346. $C_{14}H_{18}O_3N$ requires C, 52·2; H, 5·6; N, 17·4%; *M*, 322).

Hydrogen Peroxide Oxidation of "Aneurin Thiazolone."—The thiazolone (IV) (0·45 g.) was dissolved in one equivalent of N-hydrochloric acid, excess of hydrogen peroxide (100-vol.; 5 c.c.) added, and the solution warmed initially to 30° and then kept at room temperature for 18 hours. Neutralisation with N-sodium hydroxide (2 equivs.) gave the oxidation *product* (V) (0·1 g., 20%) as platelets; recrystallised from methanol it had m. p. 176° (Found: C, 45·2; H, 4·9; N, 17·6. $C_{24}H_{32}O_6N_6S_2Na_2$ requires C, 45·2; H, 5·0; N, 17·6%).

On gentle warming of the oxidation product with N-hydrochloric acid, carbon dioxide was evolved. Neither the oxidation product itself nor the decarboxylated material gave a colour with sodium nitroprusside solution.

Conversion of the Above Oxidation Product into Aneurin Disulphide.—The product (V) (0·09 g.) was dissolved in anhydrous formic acid (1 c.c.), and the solution gently warmed till evolution of carbon dioxide ceased; it was then kept at room temperature for 10 days and evaporated to dryness in a vacuum from a bath at 30°. The residue was neutralised with N-sodium hydroxide and again evaporated to dryness in a vacuum. A solution of the residue, in a minimum of water, was diluted with ethanol, filtered to remove inorganic material, diluted with a large quantity of ether, and allowed to crystallise. The

product (0·02 g.) had m. p. 177°, undepressed on admixture with a sample of aneurin disulphide (III (Found: N, 19·6. Calc. for $C_{24}H_{34}O_4N_8S_2$: N, 19·9%).

Attempted Reaction of 5-2′-Acetoxyethyl-4-methylthiazol-2-one with 4-Amino-5-bromomethyl-2-methylpyrimidine Hydrobromide.—(a) *In butanol.* 5-2′-Acetoxyethyl-4-methylthiazol-2-one (Andersag and Westphal, *Ber.*, 1937, **70**, 2035) (1·0 g.) and 4-amino-5-bromomethyl-2-methylpyrimidine hydrobromide (*idem, ibid.*) (1·42 g.) were refluxed in dry *n*-butanol for 1 hour. On concentration to half bulk, crystallisation took place; recrystallised from butanol, the *4-amino-5-butoxymethyl-2-methylpyrimidine hydrobromide* (IX; R = NH_2, R′ = OBu^n) formed extremely hygroscopic prisms (0·95 g., 69%), m. p. 138° (Found: C, 42·8; H, 6·2; N, 14·9; Br, 28·6. $C_{10}H_{18}ON_3Br$ requires C, 43·4; H, 6·5; N, 15·2; Br, 29·0%). The free base, obtained on treatment of the hydrobromide with alkali, was an oil which could not be distilled. The formation of this ether may account for the low yields of aneurin observed by Williams and Cline (*J. Amer. Chem. Soc.*, 1937, **59**, 1052) in condensation experiments with 4-amino-5-bromomethyl-2-methylpyrimidine in *n*-butanol.

(b) *In dimethylformamide.* Repetition of the above experiment in dry dimethylformamide led, on concentration *in vacuo* and cooling, to the formation of hygroscopic crystals. Very hygroscopic needles of the hydrobromide of the quaternary *salt* (VI) (0·59 g., 35%), m. p. 300° (decomp.), separated with difficulty from dry acetonitrile (Found: C, 32·5; H, 4·6; N, 17·3; Br, 46·9. $C_9H_{14}N_4Br_2$ requires C, 32·0; H, 4·1; N, 16·6; Br, 47·3%).

Reaction of 5-2′-Acetoxyethyl-2-chloro-4-methylthiazole with 4-Amino-5-bromomethyl-2-methylpyrimidine Hydrobromide.—5-2′-Acetoxyethyl-2-chloro-4-methylthiazole (Andersag and Westphal, *loc. cit.*) (1·1 g.) and 4-amino-5-bromomethyl-2-methylpyrimidine hydrobromide (1·42 g.) were refluxed in dry dioxan for 1 hour; all the pyrimidine had then dissolved and the solution showed a powerful greenish fluorescence. The solution was neutralised with dilute aqueous alkali and then evaporated to dryness under reduced pressure. The yellowish gum was extracted with dry chloroform, and the fluorescent extract evaporated till crystallisation occurred. Recrystallisation from acetone yielded *O*-acetylthiochrome (VII) (0·79 g., 52%), m. p. and mixed m. p. 118°.

O-*Acetylthiochrome* (VII).—Thiochrome (0·93 g.) was dissolved in warm acetic anhydride (20 c.c.); pyridine (0·5 c.c.) was added and the solution brought just to boiling, then kept overnight at room temperature, and excess of anhydride removed by evaporation in a vacuum. The gummy residue was dissolved in ethanol, made slightly alkaline with aqueous sodium hydroxide, and evaporated to dryness. The yellow gum crystallised from dry *n*-butanol, giving *O-acetylthiochrome* (0·61 g., 56%), which was obtained from acetone as pale yellow prisms, m. p. 118° (Found: C, 55·4; H, 5·2; N, 18·9. $C_{14}H_{16}O_3N_4S$ requires C, 55·2; H, 5·3; N, 18·5%).

Disulphide (XVII) *from 3-Benzyl-4-methylthiazolium Chloride.*—3-Benzyl-4-methylthiazolium chloride (Karimullah, *J.*, 1937, 961) (6·8 g.) (this compound forms a hydrate, colourless prisms, m. p. 136°, which on intense drying yields the anhydrous compound, m. p. 188°) was dissolved in N-sodium hydroxide solution (60 c.c., 2 equivs.). Iodine (3·8 g.), dissolved in aqueous potassium iodide solution, was added slowly to the stirred solution. The sticky resin which separated was extracted with chloroform, and the extract decolourised with thiosulphate solution. After the solution had been dried (Na_2CO_3), the solvent was removed in a vacuum, yielding a pale yellow syrup which crystallised from acetone, giving colourless leaflets of *di-*[2-(*N-benzylformamido*)*prop*-1-*enyl*] *disulphide* (5·5 g., 87%), m. p. 98° (Found: C, 63·6; H, 5·9; N, 6·8. $C_{22}H_{24}O_2N_2S_2$ requires C, 64·0; H, 5·8; N, 6·8%). This substance was recovered unchanged after being heated under reflux in solvents or heated above its m. p. for long periods.

S-p-*Nitrobenzyl Ether of "Open-chain" 3-Benzyl-4-methylthiazolium Chloride.*—3-Benzyl-4-methylthiazolium chloride (5 g.) was dissolved in aqueous sodium hydroxide solution (1·77 g. in 30 c.c.; 2 equivs.). The solution was evaporated to dryness in a vacuum in a nitrogen atmosphere, and the residue re-evaporated twice with dry toluene. The residue was then dissolved in liquid ammonia (100 c.c.) and treated with *p*-nitrobenzyl bromide (4·8 g.) suspended in liquid ammonia (150 c.c.). The dark red solution was stirred for 2 hours with exclusion of carbon dioxide and moisture, liquid ammonia being added as required to maintain the volume at 250 c.c. After being kept overnight the ammonia had evaporated and the resulting resin was warmed under reduced pressure to remove traces of ammonia, extracted with dry acetone, and filtered from the residual sodium halides. The extract was evaporated to dryness and the residue crystallised from ether. The S-p-*nitrobenzyl ether* separated from aqueous acetone as pale yellow prisms (5 g., 70%), m. p. 104° (Found: C, 62·9; H, 5·4; N, 8·1. $C_{18}H_{18}O_3N_3S$ requires C, 63·1; H, 5·3; N, 8·2%).

S-p-*Nitrobenzyl Ether* (VIII; R = p-NO_2·C_6H_4·CH_2) *of "Open-chain" Aneurin.*—Aneurin (2·5 g.) was dissolved in a little water, and sodium hydroxide solution (0·85 g. in 10 c.c.) added. This solution was evaporated to dryness in a vacuum, evaporated twice with dry toluene, and treated as before with *p*-nitrobenzyl bromide in liquid ammonia. The S-p-*nitrobenzyl ether* separated from acetone as pale yellow prisms (2 g., 66%), m. p. 203° (Found: C, 54·2; N, 5·6; N, 17·3. $C_{19}H_{22}O_3N_5S$ requires C, 54·6; H, 5·5; N, 16·8%). On treatment with sodium hydroxide, the substance rapidly blackened, sodium sulphide being formed.

The *p*-nitrobenzyl ether (0·5 g.) was refluxed for 1 hour in 10% hydrochloric acid, and the solution then evaporated in a vacuum. Extraction of the resin with hot ether and evaporation of the filtrate yielded di-*p*-nitrobenzyl disulphide (Price and Twiss, *J.*, 1909, **95**, 1728) (0·14 g., 69%), m. p. and mixed m. p. 126° (Found: N, 8·1. Calc. for $C_{14}H_{12}O_4N_2S_2$: N, 8·3%).

S-*Methyl Ether* (VIII; R = Me) *of "Open-chain" Aneurin.*—This material was obtained from aneurin (2·5 g.) as described above, the *p*-nitrobenzyl bromide being replaced by methyl iodide. It proved extremely difficult to free the product from sodium iodide; this was eventually done by precipitation as silver iodide from aqueous solution, followed by removal of the small excess of silver with

hydrogen sulphide. Care had to be taken to avoid a large excess of silver ion during the precipitation since the *S*-methylaneurin forms a sparingly soluble silver derivative which tends to separate from aqueous solution. The S-*methyl ether* separated from acetone in colourless plates (0·75 g., 34%), m. p. 133° (Found: C, 52·7; H, 6·4; N, 19·3. $C_{13}H_{20}O_2N_4S$ requires C, 52·7; H, 6·7; N, 19·0%). This compound underwent extensive decomposition when warmed with either acid or alkali.

4-*Amino*-2-*methyl*-5-*thioncarbethoxyaminomethylpyrimidine* (IX; R = NH_2, R′ = NH·CS·OEt).—4-Amino-5-aminomethyl-2-methylpyrimidine hydrochloride (2·1 g.) was dissolved in hot 95% ethanol, and sodium hydroxide (0·8 g.) in a little water was added, followed by enough water to dissolve the separated sodium chloride. Diethyl xanthate (Debus, *Annalen*, 1850, **75**, 121) (1·5 g.) was added and the whole gently refluxed for 1 hour; evolution of ethanethiol had then ceased and the product had begun to crystallise. The *thiourethane*, collected and recrystallised from methanol, formed colourless needles (1·8 g., 80%), m. p. 223° (decomp.) (Found: C, 48·1; H, 6·4; N, 25·1. $C_9H_{14}ON_4S$ requires C, 47·8; H, 6·2; N, 24·8%).

A small portion was dissolved in hot ethanol, a drop of constant-boiling hydrobromic acid added, and the solution diluted with ether till just cloudy. Colourless prisms of the *hydrobromide* separated, m. p. 179° (Found: N, 17·9. $C_9H_{14}ON_4S,HBr$ requires N, 18·1%).

3-(4-*Amino*-2-*methyl*-5-*pyrimidyl*)*methyl*-4-*phenylthiazol*-2-*one* (X).—The above thiourethane hydrochloride (1·3 g.) was suspended in dry dioxan (40 c.c.), and ω-bromoacetophenone (3 g., excess) added. The solution was gently refluxed for 7 hours, then evaporated in a vacuum to yield a red gum. This was extracted with warm acetone to remove excess of ω-bromoacetophenone, and the deliquescent residue dissolved in aqueous ethanol. The solution was made just alkaline with N-sodium hydroxide and set aside in the ice-chest. Pale yellow prisms of the *thiazolone* (0·075 g., 5%), m. p. 230°, separated from methanol (Found: C, 60·1; H, 4·6; N, 18·8. $C_{15}H_{14}ON_4S$ requires C, 60·3; H, 4·7; N, 18·8%). Heated above its m. p. for long periods this compound yielded a small quantity of weakly fluorescent thiochrome-like material.

O-*Benzyl* S-*Ethyl Xanthate*.—Freshly prepared sodium benzylxanthate (Bulmer and Mann, *J.*, 1945, 671) (62 g.) was suspended in a little ethanol, and ethyl iodide (56 g., 1·2 mols.) added. After a few minutes' warming on the steam-bath, a vigorous reaction commenced and was complete after 15 minutes. Further warming produced a marked odour of ethanethiol. The mixture was cooled, diluted with water, and extracted with ether. The pale yellow ethereal extract was well washed with water and dried (Na_2SO_4). The solvent was removed under reduced pressure and gave the product as a pale yellow oil; attempts to distil it under reduced pressure resulted in considerable decomposition, ethanethiol being produced. The yield of crude material was 45 g. (70%).

4-*Amino*-2-*methyl*-5-*thioncarbobenzyloxyaminomethylpyrimidine* (IX; R = NH_2, R′ = NH·CS·O·CH_2Ph), prepared similarly to the corresponding ethyl compound, formed colourless needles (yield, 72%), m. p. 201° from ethanol (Found: C, 58·3; H, 6·0; N, 19·6. $C_{14}H_{14}ON_4S$ requires C, 58·3; H, 5·6; N, 19·5%).

Ethyl N-(4-*Amino*-2-*methyl*-5-*pyrimidyl*)*methyl*-α-S-*phenacylthioformimidate* (as XI).—The ethyl thiourethane (1·13 g.) was suspended in ethanol (50 c.c.), and sodium (0·115 g., 1 equiv.), dissolved in ethanol (10 c.c.), was added; the solid dissolved on gentle warming. ω-Bromoacetophenone (1 g., 1 equiv.), dissolved in a little ethanol, was then added and the solution gently refluxed while a stream of nitrogen was passed through it. The solution rapidly became dark green and the colour remained after 30 minutes' refluxing but faded when the solution was allowed to cool. The mixture was then evaporated to dryness in a vacuum and the residue continuously extracted with ether for 3 hours. The extract was cooled, filtered from a little unchanged thiourethane, and extracted with N-hydrochloric acid, and the acid extract neutralised with N-sodium hydroxide. An oil separated which rapidly solidified. Recrystallised from acetone the *product* separated as colourless prisms (0·7 g., 41%), m. p. 131° (decomp.) (Found: C, 59·2; H, 5·4; N, 16·5. $C_{17}H_{20}O_2N_4S$ requires C, 59·4; H, 5·8; N, 16·3%).

A small quantity of the above compound could be obtained from reaction of the ethyl thiourethane and ω-bromoacetophenone by applying the above isolation procedure and seeding the product with authentic material.

The compound (as XI) (0·4 g.) was dissolved in dry ethanol (10 c.c.) and saturated with dry hydrogen chloride. The solution was brought to boiling for 2 minutes, kept at room temperature for one hour, then diluted with water and made alkaline with 30% sodium hydroxide solution. Pale yellow prisms of 3-(4-amino-2-methyl-5-pyrimidyl)methyl-4-phenylthiazol-2-one separated; recrystallised from methanol, the product (0·2 g., 52%) had m. p. and mixed m. p. 230° (Found: N, 18·6. Calc. for $C_{15}H_{14}ON_4S$ N, 18·8%).

The benzylthiourethane reacted with ω-bromoacetophenone in the absence of acid to yield the thiazolone (X) in 17% yield, whereas, in the presence of ethanolic hydrogen chloride, the benzyl- and the ethyl-thiourethane both gave yields of up to 80% of thiazolone. 3-Acetoxy-1-chloro-, -bromo-, and -iodo-propyl methyl ketones, α-acetyl-α-bromobutyrolactone, and bromoacetone were all too unreactive to combine with the thiourethanes even in the presence of acid catalysts, decomposition taking place at temperatures below that required for reaction. Attempts to make the thiocarbamate intermediate by treating sodium or silver salts of the thiourethane with the halogenated ketones were also unsuccessful.

S-*Phenacyl* N-*Benzylthiolcarbamate* (XII; X = O, R = H, R′ = Ph).—Benzylamine (5 g.) in ethanol (100 c.c.) was treated with a stream of carbon oxysulphide till no more solid separated. The solution was then warmed until all the solid had dissolved and ω-bromoacetophenone (5 g.) was added. The mixture was then set aside overnight at room temperature and evaporated to small bulk in a vacuum; on dilution with water, the *thiolcarbamate* crystallised. Recrystallised from aqueous ethanol (charcoal), it (3·1 g., 49%) had m. p. 132° (Found: C, 67·3; H, 5·0; N, 4·7. $C_{16}H_{15}O_2NS$ requires C, 67·3; H,

5·3; N, 4·9%). The substance was recovered unchanged on being heated to 180° for 15 minutes or refluxed in acetic anhydride for 2 hours.

A similar experiment using 3-acetoxy-1-chloropropyl methyl ketone in place of ω-bromoacetophenone led only to the production of dibenzylurea.

S-*Phenacyl* N-*Benzyldithiocarbamate* (XII; X = S, R = H, R′ = Ph).—Benzylamine (5 g.) was dissolved in ethanol (100 c.c.), and carbon disulphide (1·9 g.) added. The solution was heated to dissolve the benzylamine salt of the dithiocarbamic acid, and ω-bromoacetophenone (5 g.) added. The *dithiocarbamate* slowly separated. It formed colourless prisms (5·2 g., 74%) from ethanol and had m. p. 140° (Found: C, 63·9; H, 5·1; N, 4·7. $C_{16}H_{15}ONS_2$ requires C, 63·8; H, 5·0; N, 4·7%).

3-*Benzyl*-4-*phenylthiazol*-2-*thione* (XIII; R = Ph, R′ = H).—*S*-Phenacyl *N*-benzyldithiocarbamate (1 g.) was heated at 150° till gas evolution had ceased (*ca.* 30 minutes). Recrystallised from ethanol the thiothiazoline had m. p. 101° (yield, quantitative) (Found: C, 67·7; H, 4·8; N, 5·1. Calc. for $C_{16}H_{13}NS_2$: C, 67·9; H, 4·6; N, 5·0%). The m. p. was undepressed on admixture with an authentic specimen (von Walther and Roch, *J. pr. Chem.*, 1913, [ii], **87**, 45).

S-(3-*Acetoxy*-1-*acetylpropyl*) N-*Benzyldithiocarbamate* (XII; X = S, R = CH_2·CH_2·OAc, R′ = Me).—A mixture of benzylamine (5 g.), water (50 c.c.), and aqueous sodium hydroxide solution (2 g. in 10 c.c.) was shaken with carbon disulphide (3·8 g.) till all had dissolved. The orange solution was filtered and vigorously shaken with 3-acetoxy-1-chloropropyl methyl ketone (9 g.), a solid gradually being deposited. The *dithiocarbamate* (9 g., 60%), recrystallised from ether, had m. p. 94° (Found: C, 55·2; H, 5·3; N, 4·6. $C_{15}H_{19}O_3NS_2$ requires C, 55·3; H, 5·8; N, 4·3%).

5-2′-*Acetoxyethyl*-3-*benzyl*-4-*methylthiazol*-2-*thione* (XIII; R = Me, R′ = CH_2·CH_2·OAc).—The foregoing dithiocarbamate (1 g.) was heated at 140° till gas evolution ceased (*ca.* 5 minutes). Recrystallised from ether, the *thiazolthione* had m. p. 88° (yield, quantitative) (Found: C, 59·0; H, 5·6; N, 4·9. $C_{15}H_{17}O_2NS_2$ requires C, 58·6; H, 5·5; N, 4·6%).

3-*Acetoxy*-1-*acetylpropyl* N-(4-*Amino*-2-*methyl*-5-*pyrimidylmethyl*)*dithiocarbamate* (XIV; R = NH_2, X = S).—4-Amino-5-aminomethyl-2-methylpyrimidine hydrochloride (5·3 g.) was dissolved in water (50 c.c.), and potassium hydroxide (4·2 g.) in a little water was added, followed by carbon disulphide (1·9 g.), and the mixture was vigorously shaken until homogeneous. The orange solution was filtered to remove a little amorphous solid that had separated, 3-acetoxy-1-chloropropyl methyl ketone (4·5 g.) was added, and the mixture was shaken vigorously. Solid began to separate after 30 minutes; it was collected and crystallised from aqueous methanol, giving the *dithiocarbamate* as colourless plates (5·3 g., 60%), m. p. 250° (decomp.) (Found: C, 47·2; H, 5·3; N, 16·1. $C_{14}H_{20}O_3N_4S_2$ requires C, 47·2; H, 5·6; N, 15·8%). Treatment of the dithiocarbamate with mercuric oxide or hydrogen peroxide failed to convert it into the monothiocarbamate.

When the dithiocarbamate (1 g.) was refluxed in dry ethanol (50 c.c.) for 4 hours and the solution concentrated in a vacuum and set aside in an ice-chest, the separated solid, after recrystallisation from aqueous ethanol, was identical [m. p. and mixed m. p. 276° (decomp.)] with 1 : 2 : 3 : 4-tetrahydro-7-methyl-2-thio-1 : 3 : 6 : 8-tetra-azanaphthalene (XV; X = S) (Bergel and Todd, *J.*, 1938, 26).

S-(3-*Acetoxy*-1-*acetylpropyl*) N-(4-*Amino*-2-*methyl*-5-*pyrimidylmethyl*)*thiocarbamate* (XIV; R = NH_2, X = O).—4-Amino-5-aminomethyl-2-methylpyrimidine hydrochloride (5·3 g.) was dissolved in water (50 c.c.), potassium hydroxide (4·2 g.) in a little water was added, and carbon oxysulphide passed in from a generator for 45 minutes, the solution being continuously shaken. The solution was filtered to remove a little precipitated solid, and 3-acetoxy-1-chloropropyl methyl ketone (4·5 g.) added. The mixture was then vigorously shaken until a homogeneous solution resulted (2 hours), neutralised with acetic acid, and set aside in the ice-chest till solid separated. The *thiocarbamate* crystallised from methanol in colourless prisms (4·9 g., 58%), m. p. 240° (softening and gas evolution at 165°) (Found: C, 49·9; H, 5·9; N, 16·6. $C_{14}H_{20}O_4N_4S$ requires C, 49·5; H, 5·9; N, 16·5%).

The thiocarbamate (1 g.) was dissolved in dry ethanol (40 c.c.), and the solution gently refluxed for 4 hours, concentrated in a vacuum, and set aside in the ice-chest. The separated solid, after recrystallisation from water, was found to be sulphur-free and identical (m. p. and mixed m. p. 290°) with 1 : 2 : 3 : 4-tetrahydro-7-methyl-2-keto-1 : 3 : 6 : 8-tetra-azanaphthalene (XV; X = O). Similar results were obtained on varying the solvent employed.

1 : 2 : 3 : 4-*Tetrahydro*-7-*methyl*-2-*keto*-1 : 3 : 6 : 8-*tetra*-*azanaphthalene* (XV; X = O).—4-Amino-5-aminomethyl-2-methylpyrimidine hydrochloride (3 g.) was dissolved in water (20 c.c.), and potassium cyanate (3 g.) added. After 30 minutes, the solution was evaporated to dryness in a vacuum and the resulting solid heated to 280° for 15 minutes, no further ammonia being evolved. Recrystallised from water (charcoal), the *compound* formed colourless prisms, m. p. 290° (Found: C, 51·1; H, 4·8; N, 34·2. $C_7H_8ON_4$ requires C, 51·2; H, 4·9; N, 34·2%).

S-(3-*Acetoxy*-1-*acetylpropyl*) N-(4-*Hydroxy*-2-*methyl*-5-*pyrimidyl*)*methyldithiocarbamate* (XIV; R = OH, X = S).—5-Aminomethyl-4-hydroxy-2-methylpyrimidine hydrochloride (7 g.) was dissolved in water (50 c.c.), and sodium hydroxide (3·2 g.) in a little water was added. After addition of carbon disulphide (3·1 g.), the solution was shaken vigorously for 2 hours; 3-acetoxy-1-chloropropyl methyl ketone (7·3 g.) was then added and the shaking continued. The solution was extracted with ether to remove a little unchanged chloro-ketone and then brought to pH 7 by adding dilute acetic acid. After being kept overnight at 0°, the *dithiocarbamate* (8 g., 57%) was filtered off and recrystallised (charcoal) from aqueous ethanol; it had m. p. 174° (decomp.) (Found: C, 47·3; H, 5·3; N, 11·9. $C_{14}H_{19}O_4N_3S_3$ requires C, 47·1; H, 5·3; N, 11·8%).

5-2′-*Acetoxyethyl*-3-(4-*hydroxy*-2-*methyl*-5-*pyrimidyl*)*methyl*-4-*methylthiazol*-2-*thione* (XVI; X = S).—The above dithiocarbamate (0·5 g.) was heated at 185° till gas evolution ceased (*ca.* 15 minutes). The

pale yellow liquid set to a mass of crystals on cooling. Recrystallised from aqueous ethanol, the *thiazolthione* (0·41 g., 85%) had m. p. 185—186° (Found: C, 50·0; H, 5·1; N, 12·4. $C_{14}H_{17}O_3N_3S_3$ requires C, 49·6; H, 5·0; N, 12·4%).

S-(3-*Acetoxy*-1-*acetylpropyl*) N-(4-*Hydroxy*-2-*methyl*-5-*pyrimidyl*)*methylthiocarbamate* (XIV; R = OH, X = O).—5-Aminomethyl-4-hydroxy-2-methylpyrimidine hydrochloride (7 g.) was dissolved in water (50 c.c.), and sodium hydroxide (3·2 g. dissolved in a little water) was added. A stream of carbon oxysulphide was then passed through the solution for 40 minutes, by which time one equivalent had been absorbed. 3-Acetoxy-1-chloropropyl methyl ketone (7·3 g.) was added and the mixture shaken vigorously. The solution, which was now at pH 7, was filtered to remove some insoluble material, concentrated under reduced pressure to less than half its original bulk, and set aside. The yellow solid which separated was collected, dissolved in hot *n*-butanol, and re-precipitated by addition of ether. This process was repeated several times but the crude *thiocarbamate* (5 g.) could not be further purified. It had m. p. 130° (decomp.), followed by solidification and re-melting at *ca.* 175° (Found: N, 12·6. $C_{14}H_{19}O_3N_3S$ requires N, 12·3%).

5-2′-*Acetoxyethyl*-3-(4-*hydroxy*-2-*methyl*-5-*pyrimidyl*)*methyl*-4-*methylthiazol*-2-*one* (XVI; X = O).—The above crude thiocarbamate (0·3 g.) was heated to 150° till gas evolution ceased (15 minutes). The pale brown oil solidified when allowed to cool. Recrystallised from 95% ethanol (charcoal), the *thiazolone* formed colourless prisms, m. p. 180° (Found: C, 52·4; H, 5·5; N, 12·7. $C_{14}H_{17}O_4N_3S$ requires C, 52·1; H, 5·3; N, 13·0%).

Oxidation of the Aneurin ψ-Base.—Attempts were made to obtain the "aneurin thiazolone" (IV) by carrying out experiments in which any transiently formed aneurin ψ-base might be expected to undergo oxidation. Dropwise addition of a mixture of oxidising agent and one equivalent of alkali to a solution of aneurin in one equivalent of alkali, or of one equivalent of alkali to a mixture of aneurin and oxidising agent dissolved in one equivalent of alkali, failed to yield any trace of thiazolone. The product was always thiochrome or aneurin disulphide, depending on the oxidising agent used.

Oxidation of Aneurin (II).—Two portions of aneurin (0·005 g.) were treated with 2 and 3 equivalents of sodium hydroxide respectively, followed by excess of potassium ferricyanide. The thiochrome produced was extracted with *iso*butanol, and the solution was diluted, and the products were estimated in the usual way. The more alkaline solution showed approximately twice as much thiochrome as that to which only 2 equivalents of alkali had been added.

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UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, October 19th*, 1950.]

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114. *Substituted Benzidines and Related Compounds as Reagents in Analytical Chemistry. Part I. Solubilities of the Sulphates.*

By R. BELCHER and A. J. NUTTEN.

An examination has been made of the reactions of substituted benzidines and related compounds with the object of developing new reagents in analytical chemistry. The solubilities of the sulphates of a series of these amines have been determined in an attempt to establish possible fundamental relationships between molecular structure and solubility, and to obtain new reagents for the rapid determination of the sulphate ion.

BENZIDINE possesses three particular properties which make it a valuable reagent in analytical chemistry: (1) it is easily oxidised, (2) it forms complexes with metallic salts, (3) it forms salts with acids. In some cases, however, *e.g.*, the determination of sulphate, the reagent is not entirely satisfactory, and it seemed to us that compounds of similar structure might have advantages as analytical reagents. Accordingly, we have prepared a number of substituted benzidines and related compounds, and examined their reactions. The present paper describes the sulphate-precipitating properties of these compounds. Subsequent papers will describe further reactions and their analytical applications.

Many examples are known of decrease in solubility of complex compounds with increase in molecular weight (see Feigl, "Specific, Selective, and Sensitive Reactions," Academic Press, 1949, Chap. IX). Since the majority of the substituted benzidines and related compounds we prepared are of higher molecular weight than benzidine itself, it was thought that a weighting effect might exist, resulting in a decrease in solubility of the sulphate.

A survey of the literature revealed that several substituted benzidines and some related compounds formed difficultly soluble sulphates. In only one case, however, were solubility data given, *viz.*, *o*-tolidine sulphate (1·2 g. per l. at room temperature; Van Loon, *Chem. Zent.*, 1908, II, 1169) though naphthidine sulphate was stated to be less soluble than benzidine sulphate (Nietzki and Goll, *Ber.*, 1885, **18**, 3255).

The sulphates of several amines were prepared, and their solubilities in water determined (see table); ultimate analysis showed that in every case the normal sulphate had been obtained, but none of the sulphates examined was less soluble than benzidine sulphate. However, the following general observations can be made: (1) No weighting effect is evident; *i.e.*, increase in the weight of the molecule does not result in a decrease in solubility; some other factor may be opposing any weighting effect. (2) In general, separation of the rings in such a way that resonance between them is stopped results in a greatly increased sulphate solubility; with 4 : 4′-diaminostilbene, where resonance between the rings is maintained, a marked decrease in sulphate solubility is found. (3) Monomethylation of one of the amino-groups of benzidine results in an increase in sulphate solubility. This loss of sulphate-precipitating properties with methyl blocking is confirmed by the behaviour of *NN′*-dimethylbenzidine, which is stated by Willstätter and Kalk (*Ber.*, 1904, **37**, 3773) to have a very soluble sulphate. On the other hand, it is known that monoacetylated and monobenzoylated benzidines will give precipitates with sulphates (Hovorka, *Chem. Listy*, 1942, **36**, 113), though no solubility data are available. *NN′*-Diacetylbenzidine is described as giving only a faint precipitate under the same conditions, and it may be assumed that the sulphate of this compound is more soluble than that of monoacetylbenzidine.

Vanillylidenebenzidine has been used in the volumetric determination of sulphate (*idem, ibid.*), but from the experimental details given it would seem that the sulphate of this compound is more soluble than that of benzidine. Other mono- and di-methines derived from benzidine have been prepared (*idem, ibid.*) and these all give precipitates with sulphate. It may be concluded that condensation in this way restores the sulphate-precipitating properties of benzidine, but no solubility data are available.

Amine.	Analysis of sulphate. Found, %. C.	H.	N.	S.	Calc., %. C.	H.	N.	S.	Solubility of sulphate, g./l. at 25°.	Ref.
Benzidine	51·0	4·8	10·0	11·1	51·1	5·0	9·9	11·3	0·098	1
2-Methylbenzidine	52·8	5·4	9·2	10·5	52·7	5·4	9·5	10·8	0·342	2
3-Methylbenzidine	52·6	5·2	9·5	10·7	52·7	5·4	9·5	10·8	0·448	3
2 : 2′-Dimethylbenzidine	54·2	5·8	9·2	10·0	54·2	5·9	9·0	10·3	8·907	4
2 : 3′-Dimethylbenzidine	54·0	6·0	8·9	10·2	54·2	5·9	9·0	10·3	0·488	5
3 : 3′-Diethylbenzidine	56·7	6·7	8·3	9·4	56·8	6·6	8·3	9·5	0·429	6
3 : 3′-Diaminobenzidine	35·3	4·5	13·5	15·6	35·1	4·4	13·7	15·6	1·121	7
2-Aminodiphenyl	65·7	5·7	6·4	7·0	66·0	5·6	6·4	7·3	0·264	8
4-Aminodiphenyl	66·0	5·7	6·4	7·0	66·0	5·6	6·4	7·3	0·130	9
4-Amino-1-*p*-aminophenylnaphthalene	57·9	4·7	8·7	9·3	57·8	4·9	8·5	9·6	0·205	10
4 : 4′-Diamino-1 : 1′-dinaphthyl	62·9	4·4	7·5	8·4	62·8	4·7	7·3	8·4	0·101	11
4 : 4′-Diamino-3 : 3′-dimethyl-1 : 1′-dinaphthyl	64·6	5·2	6·6	7·7	64·4	5·4	6·8	7·8	0·162	12
2 : 7-Diaminofluorene	53·1	4·6	9·2	10·7	53·1	4·8	9·5	10·9	0·175	13
2 : 7-Diaminodiphenylene oxide	48·6	4·0	9·8	10·6	48·6	4·1	9·5	10·8	0·218	14
4 : 4′-Diaminodiphenylmethane	52·6	5·4	9·4	10·6	52·7	5·4	9·5	10·8	>10	15
4 : 4′-Diaminostilbene	54·6	5·4	8·8	10·4	54·5	5·2	9·1	10·4	0·132	16
4 : 4′-Diaminodiphenylamine	48·5	5·3	14·4	10·7	48·5	5·1	14·1	10·8	4·248	17
2-Aminodiphenylamine	61·5	5·4	11·8	6·7	61·8	5·6	12·0	6·9	1·452	18
4-Aminodiphenylamine	61·6	5·6	12·1	6·9	61·8	5·6	12·0	6·9	1·352	19
4-Aminobenzophenone	63·6	4·6	5·7	6·2	63·4	4·9	5·7	6·5	2·652	20
4 : 4′-Diaminoarsenobenzene	33·6	3·1	6·7	7·4	33·4	3·3	6·5	7·4	1·347	21
Naphthylene-1 : 2-diamine	46·9	4·5	10·8	12·2	46·9	4·7	10·9	12·5	5·516	22
Naphthylene-1 : 8-diamine	46·6	4·8	10·7	12·4	46·9	4·7	10·9	12·5	0·222	23
N-Methylbenzidine	63·3	6·2	11·5	6·2	63·1	6·1	11·3	6·5	>10	24

[1] Cf. Bisson and Christie, *Ind. Eng. Chem.*, 1920, **12**, 485 (0·096—0·098 g./l.). [2] Jacobson, *Ber.*, 1895, **28**, 2549. [3] *Idem, ibid.*, p. 2544. [4] Schultz and Rohde, *Chem. Zent.*, 1902, II, 1447. [5] Schultz, *Ber.*, 1884, **17**, 469. [6] Schultz and Flachsländer, *J. pr. Chem.*, 1902, **66**, 163. [7] Brunner and Witt, *Ber.*, 1887, **20**, 1025. [8] Fichter and Sulzberger, *Ber.*, 1904, **37**, 879. [9] *Idem, ibid.*, p. 881. [10] Bucherer and Sonnenburg, *J. pr. Chem.*, 1910, **81**, 19. [11] Cohen and Oesper, *Ind. Eng. Chem. Anal.*, 1936, **8**, 306. [12] Fries and Lohmann, *Ber.*, 1921, **54**, 2922. [13] Morgan and Thomason, *J.*, 1926, 2694. [14] Bayer, D.R.-P. 48,709. [15] King, *J.*, 1920, 992. [16] Elbs and Hoermann, *J. pr. Chem.*, 1889, **39**, 502. [17] Barbier and Sisley, *Bull. Soc. chim.*, 1905, **33**, 1233. [18] Kehrmann and Havas, *Ber.*, 1913, **46**, 342. [19] Meyer, *Ber.*, 1920, **53**, 1273. [20] Chattaway, *J.*, 1904, 395. [21] Ehrlich and Bertheim, *Ber.*, 1911, **44**, 1266. [22] Lawson, *Ber.*, 1885, **18**, 2427. [23] Hodgson and Whitehurst, *J.*, 1945, 203. [24] Rassow and Berger, *J. pr. Chem.*, 1911, **84**, 273.

Apart from the above observations, no relation between structure and solubility can be shown yet, but we hope to continue this work later.

Experimental.—The solubilities were determined as follows: The finely powdered amine sulphate was suspended in 200 ml. of distilled water, contained in a 250-ml. conical flask immersed in a thermostat at 25° (±0·1°). The contents of the flask were stirred for 72 hours by an electrically driven, rotating, glass stirrer, and then 100 ml. of the solution were filtered off and evaporated to dryness in a platinum basin on a steam-bath, and the residue was weighed.

One of us (A. J. N.) is indebted to The British Rayon Research Association for a grant enabling him to carry out the work described in this and subsequent papers.

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115. *Substituted Benzidines and Related Compounds as Reagents in Analytical Chemistry. Part II. Reaction with Oxidising Agents.*

By R. BELCHER and A. J. NUTTEN.

The sensitivities of the substituted benzidines and related compounds described in the first paper of this series towards various oxidising agents have been determined. Several amines were found to be more sensitive in their reaction than benzidine.

BENZIDINE is easily oxidised to a blue meriquinonoid compound containing one molecule of a *p*-quinonoidal oxidation product and one molecule of the base (Schlenk, *Annalen*, 1908, **363**, 313). Many applications have been found for this reaction in analytical chemistry and very sensitive tests are available for ions containing molybdenum, phosphorus, chromium, manganese, cerium, lead, and gold.

It has been claimed that two of the amines described in Part I (preceding paper) are more sensitive than benzidine in their reactions with certain oxidants. 2 : 7-Diaminofluorene is 10 times more sensitive towards persulphate than is benzidine (Schmidt and Hinderer, *Ber.*, 1932, **65**, 89), and 2 : 7-diaminodiphenylene oxide can be used with advantage in place of benzidine for the detection of ions with oxidising properties (Cullinane and Chard, *Analyst*, 1948, **73**, 95). The results of the latter workers may be summarised here, because the conditions obtaining during their sensitivity tests differ to a large extent from those employed by us. The reagents used were 0·75% solutions of benzidine and 2 : 7-diaminodiphenylene oxide in 10% (v/v) glacial acetic acid. A drop of reagent was added to a drop of neutral ion test solution, and the colour produced observed. Results given by various oxidising ions are listed in Table I. The limits of identification refer to 1 drop of test solution.

TABLE I.

Ion.	Limit of identification (μg.). Benzidine.	2 : 7-Diaminodiphenylene oxide.	Ion.	Limit of identification (μg.). Benzidine.	2 : 7-Diaminodiphenylene oxide.
Ag^{1+}	6·35	0·64	CrO_4^{2-}	0·27	0·003
Fe^{3+}	0·12	0·06	$Fe(CN)_6^{3-}$	1	0·1
Pt^{4+}	12·5	0·13	IO_4^{1-}	0·5	0·23
Au^{3+}	1	1	$S_2O_8^{2-}$	0·1	0·01
Tl^{3+}	0·04	0·04	VO_3^{2-}	1·8	0·05
Ce^{4+}	0·18	0·09	BiO_3^{1-}	0·15	0·15

No other reference to the oxidation reaction sensitivities of substituted benzidines and related compounds could be found; accordingly, the sensitivities of these compounds towards certain oxidising agents have been determined. Only those sensitivities which might be applicable in analytical chemistry are listed; for instance, naphthidine will give a direct red colour with most oxidising agents, but the reactions are not sufficiently sensitive to warrant its use for their detection.

Benzidines with substituents in the 2-position cannot be oxidised to a blue meriquinonoid compound.

The behaviour of the series of amines towards the following common cations and anions was also studied:

Ag^{1+}, Hg^{1+}, Hg^{2+}, Pb^{2+}, Cu^{1+}, Cu^{2+}, Bi^{3+}, Cd^{2+}, Fe^{2+}, Fe^{3+}, Cr^{3+}, Al^{3+}, Be^{2+}, Ti^{3+}, Ti^{4+}, Co^{2+}, Zn^{2+}, Ni^{2+}, Mn^{2+}, Zr^{4+}, Sn^{2+}, Sn^{4+}, Ba^{2+}, Ca^{2+}, Sr^{2+}, Mg^{2+}, NH_4^{1+}, Na^{1+}, Li^{1+}, Tl^{1+}, Tl^{3+}, K^{1+}, UO_2^{2+}.

PO_4^{3-}, CN^{1-}, $Fe(CN)_6^{4-}$, $Fe(CN)_6^{3-}$, F^{1-}, Cl^{1-}, Br^{1-}, I^{1-}, ClO_4^{1-}, CNS^{1-}, NO_3^{1-}, AsO_3^{3-}, AsO_4^{3-}, SbO_3^{3-}, SbO_4^{3-}, WO_4^{2-}, MoO_4^{2-}, SeO_4^{2-}, SeO_3^{2-}, TeO_4^{2-}, TeO_3^{2-}.

Certain of the amines slowly yielded precipitates with WO_4^{2-} in N-hydrochloric acid. The quantitative aspects of these reactions are being investigated and will be reported later.

The complexes which these amines form with metallic salts were not examined as they have no suitable applications in modern analytical chemistry.

The sensitivities of the amines towards oxidising agents in neutral solution were determined, with the results shown, in Table II(*a*); blue-green products were obtained except from 4-aminodiphenylamine, which gave a violet colour.

TABLE II.

Ion sensitivity, μg./ml.

	(*a*) In neutral solution.							(*b*) In acid solution.		
Amine.	MnO_4^{1-}.	$Cr_2O_7^{2-}$.	CrO_4^{2-}.	VO_3^{1-}.	$S_2O_8^{2-}$.	IO_4^{1-}.	Fe^{3+}.	VO_3^{1-}.	IO_3^{1-}.	BrO_3^{1-}.
Benzidine	0·5	5	10	10	10	40	10	10	1	—
3-Methylbenzidine	0·5	3	8	9	10	50	8	7	1	30
3 : 3′-Diethylbenzidine	0·7	4	8	10	10	60	10	10	1	30
2 : 7-Diaminofluorene	0·5	0·6	1	2	1	2	2	3	5	—
N-Methylbenzidine ...	0·75	7	10	100	3	80	10	10	1	—
4-Aminodiphenylamine	—	10	4	8	20	8	8	—	4	—

In acid solution a yellow oxidation product was formed, but again that from 4-aminodiphenylamine was violet. With the vanadate ion a more sensitive test was obtained with certain amines. Iodate and bromate ions gave this yellow colour in acid solution though they did not oxidise the amines in neutral solution. Sensitivities obtained under acid conditions are included in Table II(*b*).

Experimental.—(1) 1 Ml. of neutral ion test solution was measured into a micro-test tube, and 1 ml. of a 0·25% solution of the amine hydrochloride added. The contents of the tube were shaken and the colour formed was viewed against a white background. The ion solution was then diluted, and the procedure repeated until no colour could be detected within 30 seconds.

(2) 1 Ml. of the ion test solution in 0·1N-hydrochloric acid was treated as above with 1 ml. of amine hydrochloride solution, and the colour sensitivites determined.

DEPARTMENT OF CHEMISTRY, THE UNIVERSITY,
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116. *Substituted Benzidines and Related Compounds as Reagents in Analytical Chemistry. Part III.* 3-*Methylbenzidine and* 3 : 3′-*Diethylbenzidine as Indicators in Argentometry.*

By R. BELCHER and A. J. NUTTEN.

3-Methylbenzidine and 3 : 3′-diethylbenzidine are recommended in place of benzidine as indicators for the titration of silver solutions with bromide or iodide. The colour changes at the end-point are more satisfactory than those given by benzidine, and considerably sharper than those given by the conventional adsorption indicators; moreover, the new indicators can be used in more dilute solution.

BENZIDINE has been recommended as indicator in the titration of silver solutions with bromide (Burriel, *Anal. Soc. Fís. Quím.*, 1935, **33**, 692) and with iodide (Sierra and Burriel, *ibid.*, 1932, **30**, 366). The end-points are claimed to be superior to those obtained when the conventional adsorption indicators are used, and more dilute solutions may be titrated. Since, in general, our own experience confirmed these observations, we have examined the behaviour of the series of amines described in the preceding papers when substituted for benzidine in this reaction. In the original work benzidine acetate and benzidine sulphate were used as indicators in conjunction with copper acetate for titrations with bromide, and with copper nitrate for titrations with iodide, the colour change at the end-point being from light yellow to green and from greenish-yellow to greyish-blue, respectively.

The reaction is claimed to proceed as follows (Bnz = benzidine; X = halogen):

$$2KX + 2Cu(NO_3)_2 + H_2SO_4.Bnz \longrightarrow 2CuBnzX_2 + K_2SO_4 + 2HNO_3$$

and also by the formation of free halogen

$$2KX + 2Cu(NO_3)_2 \longrightarrow CuX_2 + 2KNO_3;\ 2CuX_2 \longrightarrow Cu_2X_2 + X_2$$

which oxidises benzidine to benzidine-blue. Both the copper benzidine complex and the benzidine-blue are adsorbed by the silver halide at the end-point.

Two substituted benzidines, 3-methyl- and 3 : 3′-diethyl-benzidine, were found to give end-points as sharp as those obtained with benzidine, and the colour changes were easier to observe. The end-points were sharp to within 1 drop and the results were comparable with those obtained when benzidine was used as indicator. Titrations were carried out with 0·1N-, 0·01N-, and 0·001N-solutions. Typical results are listed in the table.

0·1N-$AgNO_3$, taken, ml.	20	20	15	15	10	10	5	5
0·1N-KBr required, ml.	19·96	19·99	—	15·02	10·00	10·00	5·00	4·98
0·1N-KI required, ml.	19·98	20·00	15·00	14·96	9·98	9·99	4·98	5·00
0·01N-$AgNO_3$ taken, ml.	20	20	10	10				
0·01N-KBr required, ml.	19·96	19·98	10·00	9·96				
0·01N-KI required, ml.	20·00	19·96	9·96	9·98				
0·001N-$AgNO_3$ taken, ml. ...	20	20	10	10				
0·001N-KBr required, ml. ...	20·00	19·94	19·98	10·00				
0·001N-KI required, ml.	19·96	19·98	9·98	9·99				

The reverse titration could not be carried out, but when a small excess (1 or 2 drops) of bromide or iodide was added, this excess could be back-titrated with standard silver nitrate. When a larger excess of bromide or iodide was added an end-point could still be obtained on back-titration, but the colour changes were not so well-defined.

The indicators function best in neutral solution. When the hydrogen-ion concentration exceeds that corresponding to 3 ml. of 1N-acetic acid or 2 ml. of 0·1N-nitric acid in an initial volume of 20 ml. of solution, poor end-points are obtained.

Chlorides cannot be determined in this way.

Experimental.—Indicator solutions. A suspension of 0·5 g. of the sulphate of 3-methylbenzidine or 3 : 3′-diethylbenzidine in 100 ml. of a saturated solution of sodium sulphate was used.

Titration procedure. Different amounts of silver nitrate solution (as in table) were measured into a conical flask, and 1 ml. of 5% aqueous copper acetate solution and 10 drops of indicator suspension were added. The solutions were then titrated with potassium iodide or potassium bromide with continual shaking until the colour changed from yellow to blue-green.

Department of Chemistry, The University,
Edgbaston, Birmingham, 15.

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117. *Substituted Benzidines and Related Compounds as Reagents in Analytical Chemistry. Part IV. Naphthidine as Indicator in the Determination of Zinc with Ferrocyanide.*

By R. Belcher and A. J. Nutten.

Naphthidine can be used as an internal indicator in the titration of zinc with ferrocyanide and gives a more distinct colour change than any of the conventional indicators used for this purpose.

Several indicators have been recommended for the titration of zinc with ferrocyanide, but, in our hands at least, only one, *o*-dianisidine, gives a really satisfactory end-point. This indicator, first used for the titration of ferrous iron with dichromate (Weeks, *Ind. Eng. Chem. Anal.*, 1932, **4**, 127), was later recommended for the titration of zinc with ferrocyanide (Frost, *Analyst*, 1943, **68**, 51). Unfortunately, no information was supplied regarding the accuracy or precision to be expected in the latter titration.

We find that in this titration *o*-dianisidine gives results comparable with those obtained by using diphenylbenzidine (Cone and Cady, *J. Amer. Chem. Soc.*, 1927, **49**, 356; Kolthoff and Pearson, *Ind. Eng. Chem. Anal.*, 1932, **4**, 147) and that no indicator correction is necessary. The colour change (brick-red ⟶ very pale blue-green) is sharper and more easily detectable that that given by diphenylbenzidine.

Tyler (*ibid.*, 1942, **14**, 114) preferred *p*-ethoxychrysöidine to other compounds as indicator for this titration, but we were unable to obtain sharp end-points under his conditions. The present paper summarises our observations on the behaviour of several of the substituted benzidines and related compounds described in our earlier papers (*J.*, 1951 544, 546,) when used as indicators in the titration of zinc with ferrocyanide, and also describes the use of naphthidine for this purpose.

Tyler also used benzidine acetate but found it unsatisfactory as regards colour development and reproducibility.

It was found that benzidine and its 3-methyl and 3 : 3′-diethyl derivatives gave better end-points (yellow ⟶ very pale blue green) than *p*-ethoxychrysöidine or diphenylbenzidine, though not as good as *o*-dianisidine. Naphthidine, however, proved to be better than *o*-dianisidine, especially as regards the colour change (pink-red ⟶ white). No indicator correction was necessary and the indicator was completely reversible. Naphthidine has been recommended as an indicator in the titration of ferrous iron with potassium dichromate (Cohen and Oesper, *Ind. Eng. Chem. Anal.*, 1936, **8**, 306) but we have found that some destruction of the indicator occurs in this particular titration.

Experimental.—Indicator. A 1% solution of naphthidine in glacial acetic acid.

Potassium ferrocyanide solution (0·025M.). 10·557 G. of pure potassium ferrocyanide trihydrate and 0·2 g. of sodium carbonate were dissolved in distilled water, and the solution diluted to 1 litre and kept in a dark bottle.

Potassium ferricyanide solution. A 1% solution in distilled water: it should be kept in a dark bottle and discarded after 2 days.

Zinc solution (0·05M.). 3·269 G. of pure zinc dissolved in an excess of dilute sulphuric acid and diluted to 1 litre.

Titration procedure. A measured amount of zinc solution was transferred to a conical flask and dilute sulphuric acid added to make its concentration about 1N. 1 G. of ammonium sulphate was added per 50 ml. of solution. For this volume, 3 drops of ferricyanide solution and 2 drops of naphthidine indicator were added, and a 10—20% excess of ferrocyanide was run in. The flask was shaken (2—3 minutes) until the suspension became white. The excess of ferrocyanide was then titrated with standard zinc solution to a change from white to pink-red. The end-point was sharp to within 1 drop.

A selection of results is given in the table.

0·05M-Zn taken, ml.	0·025M-$K_4Fe(CN)_6$ added, ml.	Back titration: 0·05M-Zn, ml.	Total 0·05M-Zn, ml. Found.	Calc.	0·05M-Zn taken, ml.	0·025M-$K_4Fe(CN)_6$ added, ml.	Back titration: 0·05M-Zn, ml.	Total 0·05M-Zn, ml. Found.	Calc.
25	40	5·10	30·10	30·00	10	15	1·25	11·25	11·25
25	40	5·05	30·05	30·00	10	15	1·23	11·23	11·25
25	40	5·00	30·00	30·00	10	15	1·20	11·20	11·25
20	30	2·48	22·48	22·50	5	7·5	0·65	5·65	5·63
20	30	2·46	22·46	22·50	5	7·5	0·60	5·60	5·63
20	30	2·50	22·50	22·50	5	7·5	0·60	5·60	5·63
15	25	3·70	18·70	18·75					
15	25	3·78	18·78	18·75					
15	25	3·74	18·74	18·75					

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118. *Substituted Benzidines and Related Compounds as Reagents in Analytical Chemistry. Part V. New Indicators for the Microvolumetric Determination of Gold.*

By R. Belcher and A. J. Nutten.

Two new indicators, 3-methyl- and 3 : 3′-diethyl-benzidine, are recommended for use in the microtitration of gold with quinol. End-points are sharper than those obtained with *o*-dianisidine, the indicator normally used in this determination. Titration may be carried out in neutral or slightly acid solution.

Pollard (*Analyst*, 1937, **62**, 597) has used *o*-dianisidine to indicate the end-point in the titration of gold salts with quinol. Good results were obtained for the range 0·5—2 mg. of gold. Jamieson and Watson (*ibid.*, 1938, **63**, 702) have extended the method to the determination of gold in urine, where smaller amounts of the element were present.

In the above method the neutral or faintly acid gold solution was buffered with potassium bifluoride and titrated with standard quinol solution until the red colour of the indicator was discharged. We have confirmed Pollard's results but did not obtain very satisfactory end-points, the colour change being red-violet to violet. When one drop of a 1% solution of *o*-dianisidine in glacial acetic acid (rather than in dilute hydrochloric acid) was used as indicator improved end-points were obtained, but were still not entirely satisfactory.

Pollard also used *o*-tolidine as indicator in this titration but preferred *o*-dianisidine.

Some substituted benzidines and the related compound naphthidine have been used in the titration of zinc with ferrocyanide (preceding paper), and it was thought that these compounds might be substituted for *o*-dianisidine in the titration of gold salts. The following compounds gave sharper and more easily detectable end-points than *o*-dianisidine; benzidine and its 3-methyl and 3 : 3′-diethyl derivatives and 2 : 7-diaminofluorene. With the first three, the quinol solution should be added slowly near the end-point owing to the slow reaction between the gold salt and the indicator. An indication of the approach of the end-point is given by the discharge and restoration of the indicator colour. The end-point is reached when the indicator colour is not restored within 30 seconds. 2 : 7-Diaminofluorene gives a satisfactory end-point, but the indicator colour is discharged and restored with each drop of titrant, hence the titration is somewhat slower than with the other indicators.

The gold solution should be titrated immediately on addition of the indicator, because, after the solution had stood for 10 minutes, the indicator would not function. *o*-Dianisidine was found to behave similarly.

3-Methylbenzidine gave the best colour change, that with 3 : 3′-diethylbenzidine being almost as good. End-points with benzidine and 2 : 7-diaminofluorene were sharper than those obtained using *o*-dianisidine, though the discharge of the 2 : 7-diaminofluorene indicator colour during titration is a disadvantage. Results obtained are included in the table.

Indicator (and end-point).	Au present, mg.	Au found, mg.	Au present, mg.	Au found, mg.	Au present, mg.	Au found, mg.	Au present, mg.	Au found, mg.
3-Methylbenzidine (Green ⟶ pale violet)	2·00	1·98	1·50	1·50	1·00	0·98	0·50	0·50
	2·00	2·00	1·50	1·50	1·00	1·02	0·50	0·50
3 : 3′-Diethylbenzidine (Yellow-green ⟶ pale violet)	2·00	2·00	1·50	1·50	1·00	1·00	0·50	0·50
Benzidine (Yellow ⟶ pale violet)	2·00	1·99	1·50	1·50	1·00	1·00	0·50	0·50
2 : 7-Diaminofluorene (Yellow ⟶ pale violet)	2·00	2·00	1·50	1·50	1·00	0·98	0·50	0·49

Gold solutions of acid concentrations between 0·025N. and 0·25N. were also titrated. Good results were obtained, but when the acid concentration reached 0·25N., the titration had to be done very slowly owing to the slow reaction between the gold salt and the indicator. With decreasing acidity the titration could be carried out more quickly, until at 0·05N. a fairly fast drop-rate could be used. In 0·025N-acid the reaction was immediate, and titration could be effected in the usual way.

In alkaline media, a sparingly soluble compound separated, the indicator change was not easily detected, and low results were obtained.

Experimental.—Indicator solution. 1% Solution of the compound in glacial acetic acid.

Quinol solution. 0·8375 G. of quinol was dissolved in 400 ml. of water, 20 ml. of concentrated hydrochloric acid were added, and the volume was adjusted with distilled water to 1000 ml. (1 ml. ≡ 1 mg. of Au).

Gold solution. 1 G. of pure gold was dissolved with warming in 12 ml. of concentrated hydrochloric acid and 4 ml. of concentrated nitric acid. Volatile gases were then removed by bubbling air through the solution, and the volume was adjusted with distilled water to 1000 ml.

Potassium bifluoride solution. 20 G. of the salt were dissolved in distilled water, and the volume adjusted to 1000 ml. The solution was stored in a polythene bottle.

General titration procedure. Amounts of gold solution, containing between 0·5 and 2 mg. of gold, were delivered from a graduated pipette into a 150-ml. conical flask, 50 ml. of potassium bifluoride solution added, then 1 drop of indicator, and the solution titrated with standard quinol solution from a microburette until the permanent discharge of the indicator colour.

Titration of gold solutions of different acid concentrations. The gold solution was measured into a 150-ml. conical flask, 1 g. of solid potassium bifluoride added, and the volume adjusted to 50 ml. with hydrochloric acid of appropriate concentration.

DEPARTMENT OF CHEMISTRY, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM, 15.

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119. *New Syntheses of Heterocyclic Compounds. Part XII. The Condensation of Ethyl β-Aminocrotonate with Some Cyclic Amidines.*

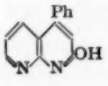
By H. ANTAKI and V. PETROW.

The base, m. p. 123°, obtained from 2-aminopyridine and ethyl acetoacetate and believed to be 2 : 10-dihydro-2-keto-4-methyl-1 : 10-diazanaphthalene (II) is now shown to be the 4-keto-2-methyl isomer (III) by its alternative synthesis from 2-bromopyridine and ethyl β-aminocrotonate.

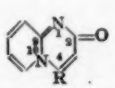
Reaction of 2-aminopyridine with ethyl β-aminocrotonate represents a novel and improved route to compounds of type (III). The reaction may be extended by employing other cyclic amidines in place of 2-aminopyridine, the ring systems (V)—(XV) being thus obtained.

BY reaction between 2-aminopyridine and benzoylacetic ester, Palazzo and Tamburini (*Atti R. Accad. Lincei*, 1911, **20**, I, 37) obtained 2-benzoylacetamidopyridine, which underwent ring closure under the action of concentrated sulphuric acid at 100° to give a compound they regarded as a 2-hydroxy-4-phenyl-1 : 8-naphthyridine (I). Acetoacetic ester likewise gave 2-acetoacetamidopyridine, m. p. 113°, but experiments on its ring closure were not reported. The reaction was subsequently re-examined by Seide (*Ber.*, 1925, **58**, 352), who obtained 4-hydroxy-6-phenylpyrimidine by oxidation of the so-called naphthyridine. Accordingly, he reformulated the latter product as a 2 : 10-dihydro-2-keto-4-phenyl-1 : 10-diazanaphthalene (II; R = Ph).

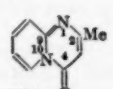
The corresponding condensation employing ethyl acetoacetate was effected by Crippa and Scevola (*Gazzetta*, 1937, **67**, 327), who heated the components in the presence of a small quantity of hydrochloric acid, obtaining a base, m. p. 123°, which they regarded as a 2 : 10-dihydro-2-keto-4-methyl-1 : 10-diazanaphthalene (II; R = Me). They postulated the initial formation



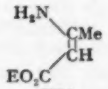
(I.)



(II.)



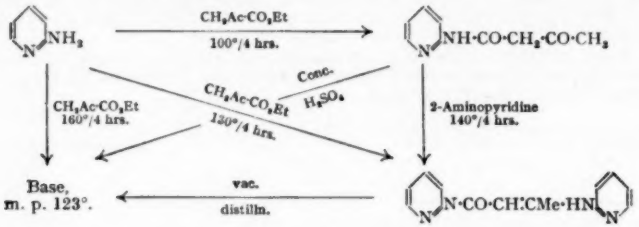
(III.)



(IV.)

of a 1 : 2 : 3 : 4-tetrahydro-2-keto-4-methyl 1 : 10-diazanaphthalene, m. p. 84°, which underwent facile dehydration on crystallisation to give the base, m. p. 123°, a result in marked contrast to the earlier observation of Palazzo and Tamburini (*loc. cit.*) (*vide supra*). The work was carried a stage further by Khitrik (*J. Gen. Chem. Russia*, 1939, **9**, 1109), who isolated a 2-acetoacetamidopyridine, m. p. 113°, by reaction of the components for 4 hours at 100°. The formulation

assigned to this compound followed from its conversion into a methiodide, a reaction which excluded the alternative 1-acetoacetylpyridone-2-imine structure from consideration. 2-Acetoacetamidopyridine passed into the pyrimidine base, m. p. 123°, in low yield on treatment with concentrated sulphuric acid. The last compound readily formed a monohydrate, m. p. 107°, in air, and a hydrate, m. p. 84°, containing $1{\cdot}25H_2O$ on crystallisation from water. β-2′-Pyridylaminocrotono-2-pyridylamide, on vacuum distillation, gave the pyrimidine base the structure of which (II; R = Me) was apparently confirmed by nitration, followed by treatment with alkali, whereupon ammonia was liberated. These preparative changes are summarised in the reaction scheme below :



By condensing ethyl acetoacetate with 2-aminopyridine, as described by Khitrik (*loc. cit.*), we readily obtained 2-acetoacetamidopyridine. The constitution assigned to this compound followed from the purple colour produced with ferric chloride. All attempts to cyclise this compound to the pyrimidine base, m. p. 123°, except by the sulphuric acid procedure described by Khitrik (*loc. cit.*), proved unsuccessful. We were thus led to question structure (II; R = Me) assigned to the base by earlier workers, and to consider its alternative formulation as 4 : 10-dihydro-4-keto-2-methyl-1 : 10-diazanaphthalene (III). The 1 : 10-diazanaphthalene structure, it should be noted, had previously been assigned by Lappin (*J. Amer. Chem. Soc.*, 1948, **70**, 3348) to the condensation products of some 2-aminopyridines with ethyl ethoxymethylenemalonate.

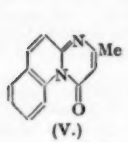
Oxidation, *per se*, cannot distinguish between structures (II) and (III) (cf. Seide, *loc. cit.*). We thus developed an unambiguous synthesis of (III), which was ultimately achieved by direct condensation of 2-bromopyridine with ethyl β-aminocrotonate (IV). The substance so obtained proved identical in every way with the pyrimidine base, m. p. 123°, prepared by Crippa and Scevola's method (*loc. cit.*) or by the pyrolytic distillation of β-2′-pyridylaminocrotono-2-pyridylamide (Khitrik, *loc. cit.*). Our failure to obtain it from 2-acetoacetamidopyridine thus receives a rational explanation. Its production by the action of concentrated sulphuric acid on the latter compound, however, is less readily interpreted unless some sort of rearrangement or formation of a pyridylaminocroton-2-pyridylamide is postulated. It is perhaps relevant to add, in this connection, that the yield of (III) obtained in this way has never exceeded 10% in our hands, and that reaction is always accompanied by evolution of gaseous products which were not identified.

Attempts to extend the chemistry of the 4 : 10-dihydro-4-keto-1 : 10-diazanaphthalene ring system have hitherto been handicapped by lack of a suitable preparative method. We now find that (III) is readily obtained in good yield by direct condensation of 2-aminopyridine with ethyl β-aminocrotonate (cf. Petrow, Rewald, and Sturgeon, *J.*, 1947, 1407). The latter reagent is indeed markedly superior to ethyl acetoacetate in reactions of this type, and its use has enabled a series of related compounds to become available for the first time.

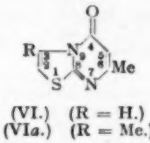
Although 2-amino-3- and -4-methylpyridine gave 1 : 4-dihydro-4-keto-2 : 8- and -2 : 7-dimethyl-1 : 4-diazanaphthalene, reaction of 2-amino-6-methylpyridine with (IV) gave only the corresponding *s*-di-(6-methyl-2-pyridyl)urea. This result is paralleled by the observations of Lappin (*loc. cit.*) that, whereas 2-amino-3- and -4-methylpyridine yield quinolizines on condensation with ethyl ethoxymethylenemalonate, the 6-methyl isomer passes smoothly into the corresponding ethyl 4-hydroxy-7-methyl-1 : 8-naphthyridine-3-carboxylate. This difference in behaviour may no doubt be attributed to steric hindrance by the 6-substituent, coupled with a shift in the tautomeric equilibrium of the cyclic amidine residue present in the 2-aminopyridine ring system. 2-Aminoquinoline likewise gave *s*-di-2-quinolylurea with ethyl 2-aminocrotonate, 4 : 12-dihydro-4-keto-2-methyl-1 : 12-diazaphenanthrene (V) being ultimately obtained by reaction of 2-chloroquinoline with (IV). 9-Aminophenanthridine, in contrast,

gave a new base which appeared to be 9 : 9′-diphenanthridylamine, but the reason for this anomalous reaction is not evident.

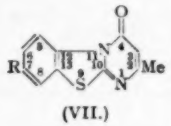
Only hydrogenated derivatives of 7 : 9-diazathionaphthen have hitherto been described in the literature (Bogert and Masters, *J. Amer. Chem. Soc.*, 1942, **64**, 2709; Whitmore, *ibid.*, 1943, **65**, 2472). By condensing 2-aminothiazole with (IV), however, we have now obtained 4 : 9-dihydro-4-keto-6-methyl-7 : 9-diazathianaphthen (VI) in excellent yield. 2-Amino-4-methylthiazole likwise gave the 3-methyl analogue (VI*a*) but the yield obtained in this instance was less favourable. Reaction of (VI) with methanolic methyl iodide led to the formation of 4 : 9-dihydro-4-keto-6-methyl-7 : 9-diazathianaphthen methiodide, but attempts to convert this into the methochloride, which was required for biological study, were only partly successful as the product gave somewhat low analytical figures for halogen. Nitration of (VI) gave a mononitro-derivative, although in somewhat poor yield. In contrast to earlier work employing ethyl acetoacetate (G.P. 603,623), condensation of 2-aminobenzthiazole with (IV) led to 4 : 11-dihydro-4-keto-2-methyl-1 : 11-diaza-9-thiafluorene (VII; R = H). The 6-chloro-, 6-amino-, 6-carbethoxy-, and 6-ethoxy-derivatives of this novel ring system were obtained in the same way. 2-Aminonaphtho(2′ : 1′-4 : 5)thiazole gave 4 : 11-dihydro-4-keto-2-methyl-



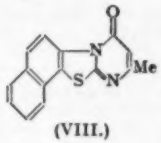
(V.)



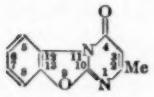
(VI.) (R = H.)
(VI*a*.) (R = Me.)



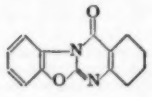
(VII.)



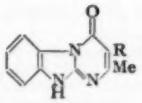
(VIII.)



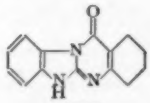
(IX.)



(X.)

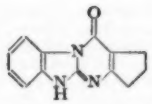


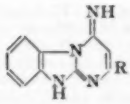
(XI.)



(XII.)

(XIII.)





(XIV; R = Me.)
(XV; R = Ph.)

7 : 8-benzo-1 : 11-diaza-9-thiafluorene (VIII). The oxygen analogue (IX) was prepared from 2-aminobenzoxazole and (IV), whilst reaction of the base with ethyl 2-keto*cyclo*hexanecarboxylate led to 4 : 11-dihydro-4-keto-2 : 3-*cyclo*hexeno-1 : 11-diaza-9-oxafluorene (X).

The formation of 4 : 11-dihydro-4-keto-2-methyl-1 : 9 : 11-triazafluorene (XI; R = H) from 2-aminobenziminazole and ethyl acetoacetate (Crippa and Perroncito, *Gazzetta*, 1935, **65**, 38) or β-aminocrotonate (Henecka, G.P. 641,593) has previously been reported. In addition to confirming this claim, we have also extended the reaction to include the 3-alkyl derivatives of this ring system, and, by employing ethyl 2-keto-*cyclo*hexanecarboxylate and -*cyclo*pentanecarboxylate as the non-basic reactants, have prepared the corresponding 2 : 3-*cyclo*hexeno- (XII) and the 2 : 3-*cyclo*penteno-analogue (XIII). When β-aminocrotononitrile and β-aminocinnamonitrile were condensed with 2-aminobenziminazole, the imino-triaza-compounds (XIV) and (XV) were obtained.

Experimental.

Microanalyses are by Drs. Weiler and Strauss, Oxford. M. p.s are uncorrected.

4 : 10-*Dihydro*-4-*keto*-2-*methyl*-1 : 10-*diazanaphthalene* (III).—(*a*) 2-Aminopyridine (9·4 g.) and ethyl β-aminocrotonate were heated for 6—8 hours at 160—180°, and then for a further hour at 200—220°. Distillation of the solid reaction product at 18 mm., followed by crystallisation from benzene–light petroleum (b. p. 100—120°), gave the *diazanaphthalene* as a hydrate, needles, m. p. 104—105°, converted into the anhydrous base, m. p. 124—125° (Found: C, 67·3; H, 5·0; N, 17·5. $C_9H_8ON_2$ requires C, 67·5; H, 5·0; N, 17·5%), after 24 hours in a vacuum-desiccator. The *picrate* formed yellow crystals (from acetone–alcohol), m. p. 184° (Found: C, 45·9; H, 2·6; N, 18·8. $C_9H_8ON_2.C_6H_3O_7N_3$ requires C, 46·2; H, 2·8; N, 18·0%). Neither the base nor the picrate gave m. p. depressions on admixture with material prepared from 2-aminopyridine and ethyl acetoacetate by Khitrik's method (*loc. cit.*).

(*b*) 2-Bromopyridine (6 g.), ethyl β-aminocrotonate (5 g.), anhydrous potassium carbonate (5 g.), and copper bronze (100—200 mg.) were heated together at 180—200° for 5—6 hours. After cooling, the

reaction product was extracted with benzene (charcoal) and treated with light petroleum (b. p. 100—120°). The yellow crystalline solid which separated was purified from benzene–light petroleum and finally from light petroleum, giving hygroscopic crystals of the anhydrous base, m. p. 124—125° (Found : C, 66·9; H, 4·9; N, 17·2%), not depressed on admixture with the product obtained by method (*a*). Its picrate, m. p. 184°, likewise gave no depression on admixture with the foregoing picrate.

(*c*) 2-Acetoacetamidopyridine was prepared by heating 2-aminopyridine (9·4 g.) and ethyl acetoacetate (26 g.) at 100° for 4 hours. Excess of the reactants was removed by distillation under reduced pressure and the solid residue crystallised from benzene–light petroleum and finally alcohol. It formed plates, m. p. 112—113° (Found : C, 60·3; H, 5·5; N, 15·9. Calc. for $C_9H_{10}O_2N_2$: C, 60·6; H, 5·6; N, 15·7%). The product so obtained was carefully added to concentrated sulphuric acid at room temperature, an exothermic reaction occurring with evolution of gas. After 24 hours the solution was poured on ice, basified with aqueous ammonia, and extracted with chloroform, evaporation of which gave (III) as needles, m. p. 123°, from benzene–light petroleum, not depressed on admixture with an authentic specimen.

1 : 4-*Dihydro*-4-*keto*-2 : 7-*dimethyl*-1 : 10-*diazanaphthalene*.—Prepared by heating 2-amino-4-methylpyridine (7 g.) and ethyl 2-aminocrotonate (8·5 g.) for 8 hours at 180—200°, this *base* formed needles from benzene–light petroleum (b. p. 60—80°), m. p. 137° (Found : C, 69·2; H, 5·6; N, 16·0. $C_{10}H_{10}ON_2$ requires C, 68·9; H, 5·7; N, 16·0%). The *picrate* separated from acetone–ethanol in a felted mass of yellow needles, m. p. 198° (Found : C, 47·4; H, 3·1; N, 17·9. $C_{10}H_{10}ON_2,C_6H_3O_7N_3$ requires C, 47·6; H, 3·2; N, 17·3%).

4 : 10-*Dihydro*-4-*keto*-2 : 8-*dimethyl*-1 : 10-*diazanaphthalene* formed needles from benzene–light petroleum (b. p. 60—80°), m. p. 130° (Found : C, 69·2; H, 5·7; N, 15·9. $C_{10}H_{10}ON_2$ requires C, 68·9; H, 5·7; N, 16·0%). The *picrate* formed yellow crystals, m. p. 154° (Found : N, 17·8. $C_{10}H_{10}ON_2,C_6H_3O_7N_3$ requires N, 17·3%).

s-*Di*-(6-*methyl*-2-*pyridyl*)*urea*.—Prepared by heating 2-amino-6-methylpyridine (10 g.) and ethyl β-aminocrotonate (12 g.) for 7—8 hours at 190°, followed by a further 2 hours at 210—220°, this *compound* formed plates [from benzene–light petroleum (b. p. 60—80°)], m. p. 194° (Found : C, 64·4; H, 5·7; N, 22·4. $C_{13}H_{14}ON_4$ requires C, 64·4; H, 5·7; N, 23·1%). The *picrate* formed yellow crystals (from acetone–ethanol), m. p. 190° (decomp.) (Found : N, 20·2. $C_{13}H_{14}ON_4,C_6H_3O_7N_3$ requires N, 20·8%).

s-*Di*-2-*quinolylurea*.—2-Aminoquinoline (5 g.) and ethyl β-aminocrotonate (5 g.) were heated at 180—200° for 6 hours. After cooling, the reaction mass was extracted with light petroleum (b. p. 100—120°) which removed unchanged 2-aminoquinoline. The residue was digested with hot alcohol, filtered, and finally crystallised from nitromethane giving the *urea* as needles, m. p. 286° (decomp.) (Found : C, 71·9; H, 4·5; N, 18·0. $C_{19}H_{16}ON_4$ requires C, 72·6; H, 4·4; N, 17·8%).

4 : 12-*Dihydro*-4-*keto*-2-*methyl*-1 : 12-*diazaphenanthrene* (V).—This *base*, forming pale yellow needles [from benzene–light petroleum (b. p. 60—80°)], m. p. 131° (Found : C, 73·8; H, 5·0; N, 13·0. $C_{13}H_{10}ON_2$ requires C, 74·4; H, 4·7; N, 13·3%), was made by heating 2-chloroquinoline (5 g.), ethyl β-aminocrotonate (4 g.), anhydrous potassium carbonate (5 g.), and a trace of copper bronze for 3 hours at 190° and for a further hour at 200—220°. The *picrate* formed yellow needles, m. p. 207° (Found : N, 15·6. $C_{13}H_{10}ON_2,C_6H_3O_7N_3$ requires N, 15·9%), from acetone–ethanol.

9 : 9′-*Diphenanthridylamine* formed yellow plates, m. p. >310° (Found : C, 83·9; H, 4·4; N, 11·2. $C_{26}H_{17}N_3$ requires C, 84·1; H, 4·5; N, 11·3%), from chlorobenzene.

4 : 9-*Dihydro*-4-*keto*-6-*methyl*-7 : 9-*diazathianaphthen* (VI) formed pale yellow needles (from benzene–light petroleum), m. p. 130° (Found : C, 50·7; H, 3·5; N, 17·3; S, 19·6. $C_7H_6ON_2S$ requires C, 50·6; H, 3·6; N, 16·8; S, 19·2%). It did not form a picrate, but gave a crystalline water-soluble sulphate and hydrochloride. The *methiodide*, prepared by heating the base (1 g.) in methanol (10 ml.) with methyl iodide (2 g.) in a sealed tube at 125° for 3 hours, formed needles, m. p. 304° (decomp.), from aqueous methanol (Found : I, 40·4. $C_8H_9ON_2SI$ requires I, 41·2%). The *nitrate*, pale yellow plates (from ethanol), m. p. 148° (decomp.) (Found : C, 36·6; H, 3·3; N, 17·7; S, 13·8. $C_7H_6ON_2S,HNO_3$ requires C, 36·4; H, 3·1; N, 18·3; S, 13·9%), separated on dilution of a solution of the base (3 g.) in nitric acid (5 ml.; *d* 1·42) with ice-water (40 ml.).

Nitration. The foregoing base (1 g.), suspended in concentrated sulphuric acid (5 ml.), was treated at 0° with an ice-cold mixture of nitric acid (1·5 ml.; *d* 1·42) and concentrated sulphuric acid (1·5 ml.), added dropwise with shaking. After 10 minutes at 0° the mixture was allowed to warm to room temperature and treated with ice-water (30 ml.), and the precipitate collected and crystallised from ethanol, yielding the x-*nitro*-derivative as yellow-brown plates, m. p. 165° (Found : C, 40·2; H, 2·4; N, 19·9; S, 14·5. $C_7H_5O_3N_3S$ requires C, 39·8; H, 2·3; N, 19·9; S, 15·1%).

4 : 9-*Dihydro*-4-*keto*-3 : 6-*dimethyl*-7 : 9-*diazathianaphthen* (VI*a*) separated from light petroleum in pale yellow needles, m. p. 136° (Found : C, 53·4; H, 4·4; N, 15·8; S, 17·4. $C_8H_8ON_2S$ requires C, 53·3; H, 4·4; N, 15·5; S, 17·7%).

4 : 11-*Dihydro*-4-*keto*-2-*methyl*-1 : 11-*diaza*-9-*thiafluorene* (VII; R = H) formed needles, m. p. 199° from light petroleum (Found : C, 61·0; H, 4·1; N, 13·2; S, 14·1. $C_{11}H_{10}ON_2S$ requires C, 61·1; H, 3·7; N, 12·9; S, 14·8%).

7-*Acetamido*-4 : 11-*dihydro*-4-*keto*-2-*methyl*-1 : 11-*diaza*-9-*thiafluorene* (VII; R = NHAc) separated from amyl alcohol in plates, m. p. 290° (Found : C, 57·2; H, 4·2; N, 15·4; S, 11·4. $C_{13}H_{11}O_2N_3S$ requires C, 57·1; H, 4·0; N, 15·4; S, 11·7%). The free base gave a *dihydrochloride monohydrate* as yellow-brown needles, m. p. >266° (decomp.), from aqueous-alcoholic hydrochloric acid (Found : C, 41·8; H, 3·8; Cl, 21·8. $C_{11}H_9ON_2S,2HCl,H_2O$ requires C, 41·0; H, 4·0; Cl, 22·0%), after hydrolysis

of the forgoing acetamido-compound (6 g.) in water (100 ml.), glacial acetic acid (20 ml.), and concentrated sulphuric acid (6 ml.) for 1 hour under reflux, basification of the resulting solution with potassium hydroxide, and precipitation of the base from hydrochloric acid with aqueous ammonia.

Ethyl 4 : 11-*Dihydro*-4-*keto*-2-*methyl*-1 : 11-*diaza*-9-*thiafluorene*-7-*carboxylate* (VII; R = CO_2Et) separated from benzene–ethanol in needles, m. p. 204—205° (Found : C, 58·1; H, 4·1; N, 9·5; S, 11·0. $C_{14}H_{13}O_3N_3S$ requires C, 58·3; H, 4·4; N, 9·6; S, 11·1%).

7-*Chloro*-4 : 11-*dihydro*-4-*keto*-2-*methyl*-1 : 11-*diaza*-9-*thiafluorene* (VII; R = Cl) formed pale yellow crystals, m. p. 220°, from benzene–ethanol (Found : C, 52·5; H, 2·9; N, 10·6; S, 12·4; Cl, 14·1. $C_{11}H_7ON_3SCl$ requires C, 52·6; H, 2·7; N, 11·1; S, 12·7; Cl, 14·1%).

7-*Ethoxy*-4 : 11-*dihydro*-4-*keto*-2-*methyl*-1 : 11-*diaza*-9-*thiafluorene* (VII; R = OEt) separated from ethanol in crystals, m. p. 198° (Found : C, 59·8; H, 4·6; N, 10·8; S, 10·6. $C_{13}H_{13}O_2N_3S$ requires C, 60·0; H, 4·6; N, 10·7; S, 12·0%).

4 : 11-*Dihydro*-4-*keto*-2-*methyl*-7 : 8-*benzo*-1 : 11-*diaza*-9-*thiafluorene* (VIII) formed crystals, m. p. 207°, from benzene (Found : C, 67·2; H, 3·3; N, 10·9; S, 10·5. $C_{15}H_{10}ON_2S$ requires C, 67·6; H, 3·7; N, 10·5; S, 12·0%).

4 : 11-*Dihydro*-4-*keto*-2-*methyl*-1 : 11-*diaza*-9-*oxafluorene* (IX) separated from benzene–light petroleum (b. p. 60—80°) in needles, m. p. 146° (Found : C, 65·7; H, 3·9; N, 14·4. $C_{11}H_8O_2N_2$ requires C, 66·0; H, 4·0; N, 14·0%).

4 : 11-*Dihydro*-4-*keto*-2 : 3-cyclo*hexeno*-1 : 11-*diaza*-9-*oxafluorene* (X), prepared by heating 2-aminobenzoxazole (2 g.) with ethyl 2-keto*cyclo*hexanecarboxylate (2·6 g.) at 180—200° for 1 hour, formed needles (from ethanol), m. p. 198° (Found : C, 69·7; H, 4·9; N, 11·8. $C_{14}H_{12}O_2N_2$ requires C, 70·0; H, 5·0; N, 11·6%).

4 : 11-Dihydro-4-keto-2-methyl-1 : 9 : 11-triazafluorene (XI; R = H), prepared from 2-aminobenziminazole and ethyl β-aminocrotonate or acetoacetate, formed needles, m. p. 294° (decomp.), from ethanol (Found : C, 66·8; H, 4·4; N, 21·4. Calc. for $C_{11}H_9ON_3$: C, 66·3; H, 4·5; N, 21·1%). The N-*acetyl* derivative formed needles, m. p. 168°, from ethanol (Found : C, 64·5; H, 4·4; N, 16·7. $C_{13}H_{11}O_2N_3$ requires C, 64·7; H, 4·5; N, 17·3%).

3-*Ethyl*-4 : 11-*dihydro*-4-*keto*-2-*methyl*-1 : 9 : 11-*triazafluorene* (XI; R = Et), prepared from 2-aminobenziminazole (1·2 gm.) and ethyl ethylacetoacetate (1·4 g.) by heating them at 130—140° until the reaction mass had solidified, formed crystals (from benzene–ethanol), m. p. 284° (decomp.) (Found : C, 68·4; H, 6·1; N, 18·4. $C_{13}H_{13}ON_3$ requires C, 68·7; H, 5·7; N, 18·5%). The 3-n-*propyl* analogue formed silvery-white plates (from benzene–ethanol), m. p. 253° (Found : C, 69·6; H, 6·3; N, 16·5. $C_{14}H_{15}ON_3$ requires C, 69·7; H, 6·2; N, 17·4%). The 3-iso*propyl* analogue, crystallised from ethanol, had m. p. 294° (Found : C, 69·3; H, 6·7; N, 17·3%).

4 : 11-*Dihydro*-4-*keto*-2 : 3-cyclo*hexeno*-1 : 9 : 11-*triazafluorene* (XII), prepared by heating 2-aminobenziminazole (1·3 g.) and ethyl 2-keto*cyclo*hexanecarboxylate (1·7 g.) at 100° until the mixture liquefied, and then at 150—160° until the mass had solidified, and crystallised from benzene–ethanol, had m. p. 296° (Found : C, 70·2; H, 5·7; N, 17·1. $C_{14}H_{13}ON_3$ requires C, 70·2; H, 5·4; N, 17·5%). The *methiodide*, prepared by heating this base (2·2 g.) with excess of methyl iodide in methanol (15 ml.) at 125° for 3 hours, formed needles, from acetone–ethanol, which decomposed at *ca.* 228° (Found : I, 23·6. $C_{15}H_{16}ON_3I$ requires I, 24·2%).

4 : 11-*Dihydro*-4-*keto*-2 : 3-cyclo*penteno*-1 : 9 : 11-*triazafluorene* (XIII), crystallised from benzene, had m. p. 304° (Found : C, 69·2; H, 5·1; N, 18·5. $C_{13}H_{11}ON_3$ requires C, 69·3; H, 4·9; N, 18·6%).

4 : 11-*Dihydro*-4-*imino*-2-*methyl*-1 : 9 : 11-*triazafluorene* (XIV).—2-Aminobenziminazole (1·3 g.) and β-aminocrotononitrile (0·83 g.) were heated at 180°. The mass liquefied, ammonia was evolved, and the product gradually solidified. Extraction with hot alcohol, followed by crystallisation from acetic acid–ethanol, gave the 4-*imino*-2-*methyl* compound, m. p. >300° (Found : C, 65·9; H, 4·7; N, 29·1. $C_{11}H_{10}N_4$ requires C, 66·7; H, 5·0; N, 28·3%). The 2-*phenyl* analogue, similarly prepared from β-aminocinnamonitrile, formed yellow crystals, m. p. >300°, from acetic acid–ethanol (Found : C, 73·3; H, 4·7; N, 21·2. $C_{16}H_{12}N_4$ requires C, 73·8; H, 4·6; N, 21·5%).

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QUEEN MARY COLLEGE (UNIVERSITY OF LONDON), E.1.
RESEARCH LABORATORIES,
THE BRITISH DRUG HOUSES, LTD., N.1.

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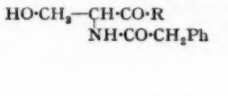
120. N-(N′-*Phenylacetylseryl*)-D-*penicillamines as Possible Biological Precursors of Benzylpenicillin.*

By Wilson Baker and W. D. Ollis.

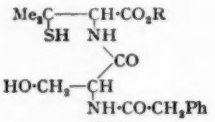
The dipeptides *N*-(*N*′-phenylacetyl-L-seryl)- and *N*-(*N*′-phenylacetyl-D-seryl)-D-penicillamine (II; R = H) have been synthesised; they do not stimulate biochemical penicillin production, and are not converted into penicillin *in vivo*. Reaction of *N*-phenylacetyl-DL-serylazide (I; R = N_3) with D-penicillamine methyl ester gave the diastereoisomeric *N*-(*N*′-phenylacetyl-L-seryl)- and *N*-(*N*′-phenylacetyl-D-seryl)-D-penicillamine methyl esters (II; R = Me) which were also prepared from the corresponding L- and D-seryl derivatives. Hydrolysis gave the related acids mentioned. Desulphurisation of these esters with Raney nickel gave *N*-(*N*′-phenylacetyl-L-seryl)- and *N*-(*N*′-phenylacetyl-D-seryl)-D-valine methyl ester respectively.

N-Phenylacetyl-DL-serylazide passes when heated into 4-phenylacetamidooxazolid-2-one (VII); the related D-serylazide gives the optically active oxazolidone.

Many different substances have been tested as possible precursors of penicillin by adding them to the culture media and determining their effect, if any, on the penicillin production (see review by Behrens, "The Chemistry of Penicillin," Princeton Univ. Press, 1949, Chapter 19, p. 657; Behrens *et al.*, *J. Biol. Chem.*, 1948, **175**, 751, 765, 771, 793; *J. Amer. Chem. Soc.*, 1948, **70**, 2837, 2843, 2849). It is well established that stimulation of the production of benzylpenicillin occurs on addition of certain compounds containing the phenylacetyl group, or of compounds which can be converted biochemically into others containing this group. Experiments with nuclear substituted phenylacetic acids, and the formation therefrom of new biosynthetic pencillins, prove that phenylacetyl groups are incorporated into the penicillin molecules. Attempts to find the precursors of the rest of the penicillin molecule have been unsuccessful.



(I.)



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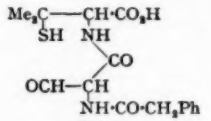
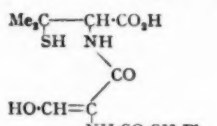


(III.)

Examination of the structure of benzylpenicillin (V) shows that it is closely related to the dipeptide *N*-(*N*′-phenylacetylseryl)-D-penicillamine (II; R = H), and the synthesis of the two diastereoisomeric forms of *N*-(*N*′-phenylacetylseryl)-D-penicillamine was undertaken because either of these substances might prove to be the biological precursor of benzylpenicillin. Oxidation of the primary alcohol group in (II; R = H) to the aldehyde (III) and subsequent cyclodehydration might give benzylpenicillin (V).



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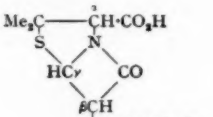

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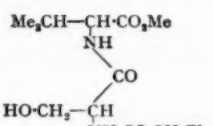


(VI.)

DL-Serine and phenylacetyl chloride gave *N*-phenylacetyl-DL-serine (I; R = OH) of which the methyl ester (I; R = OMe) was converted *via* *N*-phenylacetyl-DL-serylhydrazide (I; R = $NH{\cdot}NH_2$), characterised as its benzylidene derivative, into the corresponding azide (I; R = N_3). Reaction of this azide with D-penicillamine methyl ester in ethyl acetate solution (cf. Fruton, *J. Biol. Chem.*, 1942, **146**, 463) gave a mixture (*M*) of the two stereoisomeric forms of *N*-(*N*′-phenylacetylseryl)-D-penicillamine methyl ester (II; R = Me). This mixture

was separated into a crystalline solid (*A*) (m. p. 125°; $[\alpha]_D^{18}$ −13·0°), now known to be *N*-(*N'*-phenylacetyl-L-seryl)-D-penicillamine methyl ester, and a non-crystalline material (*B*) that was shown to consist mainly of *N*-(*N'*-phenylacetyl-D-seryl)-D-penicillamine methyl ester. These two products were identified by comparison with the substances obtained when the synthesis was repeated using first L-serine and then D-serine as the starting materials. From L-serine the synthesis proceeded smoothly and gave *N*-(*N'*-phenylacetyl-L-seryl)-D-penicillamine methyl ester (m. p. 123°). The slight discrepancy between this melting point and that of the compound obtained previously from fraction (*A*) is due to the fact that larger amounts of the latter compound were available and many recrystallisations were necessary before the final melting point of 125° was reached. That there is no difference between the crystalline methyl esters (II; R = Me) obtained from DL-serine and L-serine was proved by *X*-ray powder photographs, kindly taken by Dr. H. F. Kay and Mr. H. J. Wellard in the H. H. Wills Physical Laboratory of this University. They report as follows: "The sample, m. p. 125°, gives a powder pattern identical throughout the angular range for which reflections are observed (θ = 5—35°, using Co-K_α radiation) with that of *N*-(*N'*-phenylacetyl-L-seryl)-D-penicillamine methyl ester. It may therefore be presumed to be the latter substance." The material obtained from D-serine could not be crystallised. Comparison of its specific rotation, $[\alpha]_D^{14}$ +26·4°, with that of the non-crystalline material (*B*) ($[\alpha]_D^{20}$ +30·6°; $[\alpha]_D^{15}$ +28·7°) showed that the latter consisted mainly of *N*-(*N'*-phenylacetyl-D-seryl)-D-penicillamine methyl ester.

These identifications were further confirmed by desulphurisation with Raney nickel. *N*-(*N'*-Phenylacetyl-L-seryl)-D-penicillamine methyl ester (II; R = Me) gave *N*-(*N'*-phenylacetyl-L-seryl)-D-valine methyl ester (VI). Similarly, the non-crystalline D-seryl ester (II; R = Me) gave crystalline *N*-(*N'*-phenylacetyl-D-seryl)-D-valine methyl ester. Desulphurisation of part of fraction (*B*) gave mainly *N*-(*N'*-phenylacetyl-D-seryl)-D-valine methyl ester, but a very small amount of its diastereoisomeride was also isolated. Serine and valine, identified by paper chromatography, were formed by acid hydrolysis of these desulphurisation products.

The separation of the two diastereoisomerides formed by reaction of a D-amino-acid ester with the azide of a simple acylated racemic amino-acid does not appear to have been previously recorded. Polglase and Smith (*J. Amer. Chem. Soc.*, **1949**, **71**, 3081; see Rydon, *Ann. Reports*, **1949**, **46**, 195) have, however, shown that carbobenzyloxy-L-leucine azide and DL-alanine methyl ester gave a mixture from which the diastereoisomeric carbobenzyloxy-L-leucyl-D- and -L-alanine methyl esters were separated by crystallisation. Previously Baker and Ollis (*J.*, 1949, 345) treated the azide derived from one of the racemic forms of α-dimethoxymethyl-β-phenylacetamido-*n*-butyrylhydrazide (α-form) with D-penicillamine and isolated in a crystalline form one of the four possible stereoisomers of *N*-(α-dimethoxymethyl-β-phenylacetamido-*n*-butyryl)-D-penicillamine. Analogous resolutions have been recorded in the separation of the products of reduction of acetyldehydrophenylalanyl-L-leucine into acetyl-L- and acetyl-D-phenylalanyl-L-leucine (Behrens, Doherty, and Bergmann, *J. Biol. Chem.*, 1940, **136**, 65) and in the chromatographic separation of the two diastereoisomeric lactones produced from *N*-methyl-DL-valine and D(−)-α-bromo*iso*valeryl chloride (Cook, Cox, and Farmer, *J.*, 1949, 1028).

The stereochemistry of (II) is important when this substance is considered as a possible precursor of benzylpenicillin (V). Of the three asymmetric centres of penicillin, C and C_β may be regarded as the α-carbon atoms of penicillamine, $Me_2C(SH)\cdot CH(NH_2)\cdot CO_2H$, and of *C*-formylglycine, $CHO\cdot CH(NH_2)\cdot CO_2H$, respectively. The D-configuration of penicillamine has been established (Merck and Co., Committee for Penicillin Synthesis Reports, C.P.S., **13**, 3; **14**, 1) by conversion into a derivative of D-valine, and Merck and Co. (C.P.S., **338**, 9, 23) have shown that one of the products obtained by Raney nickel desulphurisation of sodium benzylpenicillin was *N*-(*N'*-phenylacetyl-L-alanyl)-D-valine. These results prove that C_α and C_β have D- and L-configurations respectively, and this was confirmed by *X*-ray investigation (Crowfoot, Bunn, Rogers-Low, and Turner-Jones; "The Chemistry of Penicillin," Chapter 11, p. 310).

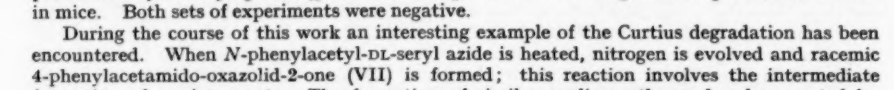
As far as the synthesis of penicillin is concerned, if the β-lactam ring and the thiazolidine ring are *cis* to one another, and if the intermediates are such that C_α and C_β have the correct configuration, then there are only two possible configurations for the molecule that is formed.

It is possible, therefore, that if *N*-(*N'*-phenylacetyl-L-seryl)-D-penicillamine was oxidised to give (III), then this *N*-benzylpenaldyl-D-penicillamine might cyclise to give a product with the required configurations at C_α and C_β. *N*-(*N'*-Phenylacetyl-L-seryl)-D-penicillamine methyl ester (II; R = Me) was hydrolysed under mild conditions by aqueous alkali to the corresponding acid (II; R = H) which was kindly tested by Dr. E. P. Abraham of the Sir William Dunn School of Pathology, Oxford, as a possible precursor in the biosynthesis of penicillin. It was

found that it did not stimulate or increase the yield of penicillin produced by *P. notatum*, nor when injected into mice did it cause any antibiotic to be excreted in the urine.

N-(*N*′-Phenylacetyl-D-seryl)-D-penicillamine was also tested as a possible biological precursor because biochemical oxidation of the primary alcohol group of a D-seryl moiety might occur, although that of an L-seryl fragment might be unaffected. The conversion of *N*-(*N*′-phenylacetyl-D-seryl)-D-penicillamine (II; R = H) into (V) with the L-configuration for C_β would require an optical inversion This could take place if an equilibrium involving the enolic form (IV) was established. In order to test this hypothesis a mixture (mixture *M*; see above) of *N*-(*N*′-phenylacetyl-L-seryl)- and *N*-(*N*′-phenylacetyl-D-seryl)-D-penicillamine methyl esters was hydrolysed and the mixture of free acids was converted into sodium salts. Through the kindness of Sir Jack Drummond, of Boots Pure Drug Company, Nottingham, to whom we express our thanks, this substance was tested both as a precursor in normal penicillin production by *P. chrysogenum* Q.176, and as a precursor *in vivo* against streptococcal infection in mice. Both sets of experiments were negative.

During the course of this work an interesting example of the Curtius degradation has been encountered. When *N*-phenylacetyl-DL-seryl azide is heated, nitrogen is evolved and racemic 4-phenylacetamido-oxazolid-2-one (VII) is formed; this reaction involves the intermediate formation of an *iso*cyanate. The formation of similar cyclic urethanes has been noted by others (Schroeter, G.P. 220,852, "Friedländer," 1910—1912, **10**, 1309; Fruton, *J. Biol. Chem.*,



(VII.)

1942, **146**, 463; Newman, *J. Amer. Chem. Soc.*, 1949, **71**, 378). When the azide (I; R = N_3) derived from *N*-phenylacetyl-D-serylhydrazide is heated, the oxazolidone obtained is optically active ($[\alpha]_D^{20}$ +127°); no trace of the racemic compound was detected. This result is similar to the results obtained by others on the Curtius degradation of optically active azides (Kenyon *et al.*, *J.*, 1941, 263; 1946, 25) and shows that the rearrangement is intramolecular, since the asymmetric groups retain their configuration during migration. The high specific rotation of the active oxazolid-2-one is in agreement with the generalisation made by Neuberger (" Advances in Protein Chemistry," 1948, **4**, 305) that cyclic compounds derived from optically active amino-acids where the asymmetric carbon is part of a ring system have large optical rotatory powers.

Experimental.

(M. p.s are uncorr. Microanalyses are by Mr. W. M. Eno, Bristol, and Drs. Weiler and Strauss, Oxford).

N-Phenylacetyl-DL-serine (I; R = OH).—To a vigorously stirred solution of DL-serine (42 g.) in 2N-sodium hydroxide (300 c.c.) and water (100 c.c.) cooled in ice, phenylacetyl chloride (105 c.c.) and 2N-sodium hydroxide (920 c.c.) were added simultaneously during 2 hours so that the solution remained alkaline throughout. After being stirred for a further hour, the mixture was shaken with ether (500 c.c.), acidified with 2N-hydrochloric acid, and left overnight in a refrigerator. The solid was collected, dried, washed with cold benzene (350 c.c.), and crystallised from hot water, giving *N*-phenylacetyl-DL-serine (69 g.), m. p. 128°. Concentration of the mother-liquors and crystallisation of the product gave a further quantity (16 g.) of the acid (total yield, 96%). The united crops were recrystallised from benzene–ethanol and gave *N*-phenylacetyl-DL-serine as colourless, rhombic crystals, m. p. 131° (Found: C, 59·8; H, 6·0; N, 5·7. Calc. for $C_{11}H_{13}O_4N$: C, 59·2; H, 5·9; N, 6·3%). A less easy method for preparing this substance is given in " The Chemistry of Penicillin " (Chapter 4, p. 71).

N-Phenylacetyl-DL-serine Methyl Ester (I; R = OMe).—This esterification was carried out in a Soxhlet apparatus with anhydrous magnesium sulphate in the thimble. A mixture of *N*-phenylacetyl-DL-serine (22·3 g.), absolute methanol (200 c.c.), anhydrous benzene (50 c.c.), and concentrated sulphuric acid (2 c.c.) was boiled under reflux for 6 hours. After addition of water (1 c.c.), potassium hydrogen carbonate was added until the solution was neutral to Congo-red, and the solvents were removed under diminished pressure. The residue was dissolved in chloroform (150 c.c.), washed with water, and dried ($MgSO_4$), and removal of the chloroform then gave *N*-phenylacetyl-DL-serine methyl ester (22·4 g., 95%) as a colourless oil.

N-Phenylacetyl-DL-seryl Hydrazide (I; R = NH·NH_2).—Hydrazine hydrate (96%; 9·6 c.c.) was added to *N*-phenylacetyl-DL-serine methyl ester (22·4 g.), a crystalline precipitate rapidly separating. After 20 hours, excess of hydrazine was removed under diminished pressure over concentrated sulphuric acid, and crystallisation of the residue (22·4 g., 100%) from aqueous ethanol gave *N-phenylacetyl-DL-serylhydrazide* (16·8 g.) as fine, white needles, m. p. 175° (Found: C, 56·1; H, 6·4; N, 18·2. $C_{11}H_{15}O_3N_3$ requires C, 55·7; H, 6·3; N, 17·7%).

Benzylidene derivative. Benzaldehyde (0·4 c.c.) in ethanol (1·5 c.c.) was added to a solution of this hydrazide (0·5 g.) in water (2 c.c.), and the mixture warmed on a steam-bath for 1 minute. Next day the solid (0·68 g., 100%) was collected and crystallised from *n*-butanol (60 c.c.) giving the *benzylidene* derivative (0·61 g.) as a white, micro-crystalline powder, m. p. 207° (Found: C, 66·6; H, 5·9; N, 12·8. $C_{18}H_{19}O_3N_3$ requires C, 66·5; H, 5·9; N, 12·9%).

Reaction of N-*Phenylacetyl-*DL-*serylazide with* D-*Penicillamine Methyl Ester. Isolation of* N-(N′-*Phenylacetyl-*L-*seryl)- and* N-(N′-*Phenylacetyl-*D-*seryl)-*D-*penicillamine Methyl Ester* (II; R = Me).—A solution of sodium nitrite (6·05 g.) in water (80 c.c.) was added with stirring to a solution of *N*-phenylacetyl-DL-serylhydrazide (18·9 g.) in 0·5N-hydrochloric acid (225 c.c.) at 0°. The azide was immediately extracted into ethyl acetate (50 c.c., 25-c.c., and 25-c.c. portions), the combined extracts were washed with 5% aqueous sodium hydrogen carbonate and filtered through anhydrous magnesium sulphate into a solution of D-penicillamine methyl ester (14·1 g.) in ethyl acetate (25 c.c.). All these operations were carried out very rapidly and it was found important to keep the temperature of the solutions close to 0°. After 24 hours at room temperature the ethyl acetate solution was washed with 2N-hydrochloric acid (2 × 25 c.c.), 5% aqueous sodium hydrogen carbonate (25 c.c.), and water (25 c.c.), then dried ($MgSO_4$), and the solvent removed under reduced pressure in an atmosphere of nitrogen, leaving a light yellow oil (24·5 g., 84%), $[\alpha]_D^{25}$ +14·2° (*c*, 5·0 in methanol), which did not crystallise. This oil was dissolved in hot benzene (90 c.c.) and filtered. From a portion (30 c.c.) of the filtrate the solvent was removed under reduced pressure and the residue (*M*) (8·0 g.) was hydrolysed (see below). The remainder of the filtrate was slowly cooled and crystallisation induced by seeding. The crystalline precipitate (7·2 g.), $[\alpha]_D^{20}$ −10·7° (*c*, 3·5 in methanol), m. p. 95—110°, was collected, washed with cold benzene (15 c.c.), and dried (Fraction *A*). Removal of the benzene from the filtrate gave a light yellow glass (Fraction *B*; 10·2 g.), $[\alpha]_D^{20}$ +30·6° (*c*, 3·1 in methanol), $[\alpha]_D^{15}$ +28·7° (*c*, 3·4 in methanol).

Fraction (*A*) was recrystallised twice from benzene (50—100 c.c.) and gave short, colourless needles (6·05 g.), m. p. 122—123°, $[\alpha]_D^{18}$ −12·9° (*c*, 2·6 in methanol). Recrystallisation from ethanol (30 c.c.)–water (60 c.c.) gave N-(N′-*phenylacetyl-*L-*seryl)-*D-*penicillamine methyl ester* (5·5 g.) as long, colourless needles, m. p. 125°, $[\alpha]_D^{18}$ −13·0° (*c*, 2·5 in methanol) (Found: C, 55·4; H, 6·5; N, 7·4; S, 8·5; OMe, 8·0. $C_{17}H_{24}O_5N_2S$ requires C, 55·4; H, 6·5; N, 7·6; S, 8·7; OMe, 8·4%). A mixed m. p. with an authentic specimen of *N*-(*N*′-phenylacetyl-L-seryl)-D-penicillamine methyl ester (see below) showed no depression and the two substances gave identical *X*-ray powder photographs.

Fraction (*B*) could not be obtained crystalline, and an attempted purification by chromatography of a benzene solution on an alumina column and elution with benzene–ethanol (95 : 5) was not successful. The optical rotation (above) and Raney nickel desulphurisation (see below) showed that it consisted mainly of *N*-(*N*′-phenylacetyl-D-seryl)-D-penicillamine methyl ester.

Hydrolysis of Mixture of Diastereoisomers (*M*).—Mixture (*M*) (8 g.) (above) consisting of *N*-(*N*′-phenyl-L-seryl)- and *N*-(*N*′-phenylacetyl-D-seryl)-D-penicillamine methyl ester was hydrolysed as described for *N*-(*N*′-phenylacetyl-L-seryl)-D-penicillamine methyl ester (see below), giving a non-crystalline mixture of *N*-(*N*′-phenylacetyl-D-seryl)- and *N*-(*N*′-phenylacetyl-L-seryl)-D-penicillamine (6·70 g.). These acids were converted into their sodium salts by dissolution in 2N-sodium carbonate (9·5 c.c.) to give a solution of pH 6, then "freeze-drying" to give the sodium salts as a cream-coloured powder. This was the material used in the laboratories of Boots Pure Drug Company to determine its effect on the yield of penicillin when added to the culture-medium.

N-*Phenylacetyl-*L- *and* N-*Phenylacetyl-*D-*serine* (I; R = OH).—DL-Serine (*Org. Synth.*, 1940, **20**, 81) was resolved as described by Fischer and Jacobs (*Ber.*, 1906, **39**, 2942). Phenylacetyl chloride (11·2 c.c.) and 2N-sodium hydroxide (83 c.c.) were added simultaneously to a stirred solution, at 0°, of L-serine (5 g.) in N-sodium hydroxide (47 c.c.) during half an hour at 0°. After a further 10 minutes, the mixture was filtered, acidified with concentrated hydrochloric acid (20·2 c.c.), and kept in a refrigerator overnight. The precipitate was collected, dried, and washed with a small amount of cold benzene to remove phenylacetic acid. Crystallisation from water gave *N-phenylacetyl-*L-*serine* (1·8 g.) as colourless, rectangular prisms, m. p. 132° (Found: C, 58·9; H, 5·6; N, 6·4. $C_{11}H_{13}O_4N$ requires C, 59·2; H, 5·8; N, 6·3%).

Similarly, D-serine gave *N*-phenylacetyl-D-serine, m. p. 132°.

N-*Phenylacetyl-*L- *and* N-*Phenylacetyl-*D-*serine Methyl Ester* (I, R = OMe).—A mixture of *N*-phenylacetyl-L-serine (1·5 g.), absolute methanol (20 c.c.), anhydrous benzene (5 c.c.), and concentrated sulphuric acid (0·15 c.c.) was refluxed for 2·75 hours in a Soxhlet apparatus, and worked up as in the case of the DL-derivative, to give *N*-phenylacetyl-L-serine methyl ester (1·35 g., 85%) as a light yellow oil.

N-Phenylacetyl-D-serine methyl ester was prepared similarly.

N-*Phenylacetyl-*L-*serylhydrazide* (I; R = $NH{\cdot}NH_2$).—A mixture of *N*-phenylacetyl-L-serine methyl ester (1·35 g.) and 96% hydrazine hydrate (0·65 c.c.) in ethanol (2 c.c.) was left at room temperature for 18 hours. The precipitate (1·0 g., 75%) was collected and crystallised from ethanol (25 c.c.) and water (1·0 c.c.), giving N-*phenylacetyl-*L-*serylhydrazide* (0·76 g.) as colourless needles, m. p. 199°, $[\alpha]_D^{15}$ −39·3° (*c*, 1·1 in water) (Found: C, 56·0; H, 6·4; N, 17·7. $C_{11}H_{15}O_3N_3$ requires C, 55·7; H, 6·3; N, 17·7%). The *benzylidene* derivative (80% yield), prepared as in the previous case, formed colourless platelets (from benzene–ethanol), m. p. 196° (Found: C, 66·8; H, 5·9; N, 13·1. $C_{18}H_{19}O_3N_3$ requires C, 66·5; H, 5·9; N, 12·9%).

N-*Phenylacetyl-*D-*serylhydrazide.*—This *compound* was prepared similarly from *N*-phenylacetyl-D-serine methyl ester and 96% hydrazine hydrate, and crystallised from slightly diluted ethanol as needles, m. p. 199°, $[\alpha]_D^{16}$ +39·1° (*c*, 1·2 in water) (Found: C, 55·9; H, 6·3; N, 18·0%). The *benzylidene* derivative formed colourless platelets from benzene–ethanol, m. p. 196° (Found: C, 67·0; H, 6·4; N, 13·2%).

N-(N′-*Phenylacetyl-*L-*seryl)-*D-*penicillamine Methyl Ester* (II; R = Me).—The azide was prepared as before from *N*-phenylacetyl-L-serylhydrazide (500 mg.) in 0·5N-hydrochloric acid (5·9 c.c.) and sodium nitrite (160 mg.) in water (2 c.c.). A solution of this azide in ethyl acetate (20 c.c.) was added to D-penicillamine methyl ester (850 mg.) in ethyl acetate (4 c.c.). Next day the solution was worked up as in the reaction of *N*-phenylacetyl-DL-serylazide and gave a gummy residue (620 mg., 80%). Crystallisation from benzene–light petroleum (b. p. 60—80°) gave a solid (470 mg.) which was

recrystallised five times from benzene (1 c.c.) and twice from aqueous ethanol, giving N-(N′-*phenylacetyl*-L-*seryl*)-D-*penicillamine methyl ester* as colourless needles, m. p. 123° (Found: C, 55·7; H, 6·6; N, 7·8; S, 8·3; OMe, 9·1. $C_{17}H_{24}O_5N_2S$ requires C, 55·4; H, 6·5; N, 7·6; S, 8·7; OMe, 8·4%).

N-(N′-*Phenylacetyl*-L-*seryl*)-D-*penicillamine* (II; R = H).—*N*-(N′-Phenylacetyl-L-seryl)-D-penicillamine methyl ester (0·3 g.) was dissolved in pure dioxan (3 c.c.) and after the addition of thymol-violet (pH range 9·0—13·0) the solution was rapidly titrated with N-sodium hydroxide until the solution was faintly blue (this required almost exactly one equivalent: calc., 0·81 c.c.; found, 0·82 c.c.). Two more equivalents of N-sodium hydroxide (1·64 c.c.) were added and after the solution had been kept at room temperature for 30 hours it was neutralised with N-hydrochloric acid, freed from dioxan under diminished pressure, and extracted with ethyl acetate (one 6-c.c. and two 3-c.c. portions). The combined ethyl acetate extracts were extracted with 5% sodium hydrogen carbonate solution (two 3-c.c. portions) which, after being washed with ether, was acidified with 2N-hydrochloric acid and the liberated acid was extracted into ethyl acetate. After drying ($MgSO_4$), the final ethyl acetate extract gave the hygroscopic, non-crystalline N-(N′-*phenylacetyl*-L-*seryl*)-D-*penicillamine* (213 mg., 74%) (Found: C, 53·0; H, 6·1; N, 7·4; S, 8·1%; equiv., 316. $C_{16}H_{22}O_5N_2S$ requires C, 54·25; H, 6·2; N, 7·9; S, 9·0%; equiv., 354). This material gave a strong, transient blue ferric chloride reaction. It could not be crystallised, nor could crystalline salts be obtained.

N-(N′-*Phenylacetyl*-D-*seryl*)-D-*penicillamine Methyl Ester*.—Conversion of *N*-phenylacetyl-D-seryl-hydrazide (0·5 g.) into its azide, and reaction of this with D-penicillamine methyl ester as in the previous case, gave a gummy residue (583 mg., 75%). This was dissolved in benzene (2 c.c.), and light petroleum (b. p. 60—80°) was added until the solution was slightly cloudy. After being kept in a refrigerator overnight, the solution was filtered and the small amount of solid was discarded. Removal of the solvent gave N-(N′-*phenylacetyl*-D-*seryl*)-D-*penicillamine methyl ester* as a colourless gum, $[\alpha]_D^{24}$ +26·4° (*c*, 2·8 in methanol), which could not be crystallised (Found: C, 55·5; H, 6·6; N, 7·5; S, 9·0; OMe, 8·6%).

Raney Nickel Desulphurisation of N-(N′-*Phenylacetyl*-L-*seryl*)-D-*penicillamine Methyl Ester. Formation of* N-(N′-*Phenylacetyl*-L-*seryl*)-D-*valine Methyl Ester* (VI).—A mixture of *N*-(N′-phenylacetyl-L-seryl)-D-penicillamine methyl ester (1 g.), Raney nickel (*ca.* 12 g.), and methanol (75 c.c.) was heated under reflux for 2·5 hours, cooled, and filtered, and the nickel well washed with methanol. The filtrate and washings were combined, the methanol was removed under diminished pressure, the crystalline residue dissolved in methanol (15 c.c.), and water (15 c.c.) added. After being kept in the refrigerator overnight, the precipitate (679 mg.), m. p. 164°, was collected; addition of water to the mother-liquors gave a further precipitate (56 mg.), m. p. 164°. The total yield (735 mg., 81%) was recrystallised from aqueous methanol, giving N-(N′-*phenylacetyl*-L-*seryl*)-D-*valine methyl ester* as colourless needles, m. p. 164·5°, $[\alpha]_D^{24}$ −6·7° (*c*, 1·0 in methanol) (Found: C, 61·1; H, 7·0; N, 8·7; OMe, 9·2. $C_{17}H_{24}O_5N_2$ requires C, 60·7; H, 7·2; N, 8·3; OMe, 9·2%). The identity of this dipeptide was confirmed by hydrolysing a small amount with concentrated hydrochloric acid for 2 hours at 100°. The acid was removed by heating the solution under reduced pressure, adding water to the residue, and removing it by distillation. This was repeated several times. The residue was analysed by paper partition chromatography, using Whatman No. 1 filter paper and as solvent mixture *n*-butanol (480 c.c.), water (195 c.c.), acetic acid (95 c.c.), and *n*-butyl acetate (35 c.c.). Two spots due to serine (R_F = 0·11) and valine (R_F = 0·42) were detected and this behaviour was exactly paralleled by a mixture of these two amino-acids.

Raney Nickel Desulphurisation of N-(N′-*Phenylacetyl*-D-*seryl*)-D-*penicillamine Methyl Ester. Formation of* N-(N′-*Phenylacetyl*-D-*seryl*)-D-*valine Methyl Ester* (VI).—Desulphurisation of *N*-(N′-phenylacetyl-D-seryl)-D-penicillamine methyl ester (263 mg.) was carried out with Raney nickel (*ca.* 5 g.) and methanol (20 c.c.) as in the previous case. Removal of the methanol gave a non-crystalline residue (226 mg.) that was dissolved in ethyl acetate (20 c.c.), washed with 2N-hydrochloric acid and 2N-sodium carbonate, then dried ($MgSO_4$), and the solvent removed, giving a partly crystalline residue (151 mg.). This was triturated with light petroleum (b. p. 60—80°), and the microcrystalline solid (115 mg., m. p. 75—80°) collected. Recrystallisation from benzene (4 c.c.)–light petroleum (b. p. 60—80°; 4 c.c.) gave N-(N′-*phenylacetyl*-D-*seryl*)-D-*valine methyl ester* as fine, colourless needles, m. p. 95°, $[\alpha]_D^{25}$ +46° (*c*, 0·35 in methanol) (Found: C, 61·2; H, 7·4; N, 8·5; OMe, 9·0%). The identity of this dipeptide ester was confirmed by paper partition chromatography (see above) by comparison of its acid hydrolysate with an artificial mixture of serine and valine.

Raney Nickel Desulphurisation of Fraction B. *Formation of* N-(N′-*Phenylacetyl*-L-*seryl*)- *and* N-(N′-*Phenylacetyl*-D-*seryl*)-D-*valine Methyl Ester* (VI).—Desulphurisation of fraction *B* (1·3 g.) was carried out with Raney nickel (*ca.* 12 g.) in methanol (80 c.c.) as in the previous cases. After removal of the Raney nickel and the methanol, the remaining oil (1·1 g.) was dissolved in methanol (15 c.c.), and water (40 c.c.) added. After being kept in the refrigerator overnight the precipitate (fraction *X*; m. p. 133—139°; 259 mg.) was collected and dried. Water was added to the filtrate, which was then extracted with ethyl acetate (2 × 20 c.c.), then dried ($MgSO_4$), and the solvent removed, leaving an oil which crystallised on trituration with light petroleum; the solid was collected (fraction *Y*; m. p. 82—84°; 550 mg.). Fraction *X*, after three recrystallisations from aqueous methanol, gave *N*-(N′-phenylacetyl-L-seryl)-D-valine methyl ester (10 mg.), m. p. 162° (mixed m. p. with an authentic specimen 163·5°). Fraction *Y* was recrystallised six times from benzene–light petroleum (b. p. 60—80°) and eventually gave *N*-(N′-phenylacetyl-D-seryl)-D-valine methyl ester (190 mg.) as colourless needles, m. p. and mixed m. p. 95°.

Racemic 4-*Phenylacetamido-oxazolid*-2-*one* (VII).—Sodium nitrite (0·735 g.) in water (15 c.c.) was added to a solution of *N*-phenylacetyl-DL-serylhydrazide (2·3 g.) in 0·5N-hydrochloric acid (26·2 c.c.) with stirring at 0°. The azide was extracted into ethyl acetate (2 × 15 c.c.) and the combined extracts were quickly washed with water (5 c.c.) and filtered through anhydrous magnesium sulphate. The filtrate was kept at 40° for 20 minutes, then for a further 10 minutes with the temperature rising to 60°.

Nitrogen was evolved and the crystalline precipitate (1·67 g., 78%) which separated was collected and crystallised from water, giving racemic *4-phenylacetamido-oxazolid-2-one* as colourless needles, m. p. 184° (Found: C, 59·8; H, 5·4. $C_{11}H_{12}O_3N_2$ requires C, 60·0; H, 5·4%).

dextro- *and* lævo-*4-Phenylacetamido-oxazolid-2-one* (VII).—The *dextro*-compound was prepared as in the previous case by heating the ethyl acetate (4 c.c.) solution of the azide obtained by adding sodium nitrite (33 mg.) in water (0·4 c.c.) to *N*-phenylacetyl-D-serylhydrazide (100 mg.) in 0·5N-hydrochloric acid (1·2 c.c.). The crystalline precipitate (71 mg., 77%) obtained by adding light petroleum (b. p. 60—80°) to the ethyl acetate solution and cooling was collected. Crystallisation from water (2 c.c.) gave dextro-*4-phenylacetamido-oxazolid-2-one* as colourless needles, m. p. 157°, $[\alpha]_D^{20}$ +127° (*c*, 0·1 in water) (Found: C, 60·1; H, 5·4; N, 12·6%). Similarly *N*-phenylacetyl-L-serylhydrazide (100 mg.) gave lævo-*4-phenylacetamido-oxazolid-2-one* (68 mg., 73%) as colourless needles, m. p. 157° (Found: C, 60·2; H, 5·5; N, 13·0%).

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THE UNIVERSITY, BRISTOL. [*Received, October 27th*, 1950.]

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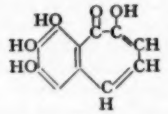
121. *Purpurogallin. Part IV. Some Properties of Tropolones.*

By ROBERT D. HAWORTH and JOHN D. HOBSON.

An improved preparation of 2-carboxy-4-hydroxy-3-keto*cyclo*heptatrienylacetic acid (II; R = R′ = R″ = H) and 2-hydroxy-6-methyl*cyclo*heptatrienone (IV; R = H; R′ = Me) from purpurogallin is recorded. Isomeric methyl and *p*-nitrobenzyl ethers of (IV; R = H; R′ = Me) have been prepared; oxidation of the former to 6-formyl-2-hydroxy*cyclo*heptatrienone (IV; R = H; R′ = CHO) and the corresponding 6-carboxylic acid is described, and decarboxylation of the latter has yielded the parent 2-hydroxy*cyclo*heptatrienone (tropolone) (IV; R = R′ = H). Some substitution reactions of the tropolones are described, and some ultra-violet and infra-red spectroscopic results are included together with a brief discussion of the tropolone ring system.

IN Part I (*J.*, 1948, 1045) it was shown that alkaline solutions of purpurogallin (I) were oxidised by an air-stream to α-carboxy-β-carboxymethyltropolone (2-carboxy-4-hydroxy-3-keto*cyclo*heptatrienylacetic acid) (II; R = R′ = R″ = H)* which, when heated above its melting point, was converted into β-methyltropolone (2-hydroxy-6-methyl*cyclo*heptatrienone) (IV; R = H, R′ = Me) by loss of two molecular proportions of carbon dioxide. As structure (I) for purpurogallin has since been confirmed synthetically (*Chem. and Ind.*, 1950, 149; *J.*, 1950, 1631), structures (II; R = R′ = R″ = H) and (IV; R = H, R′ = Me) are securely established, and their preparation from purpurogallin represents a synthesis of representatives of the 2-hydroxy-*cyclo*heptatrienone (tropolone) (Dewar, *Nature*, 1945, **155**, 50, 141, 479) group. It has been found that the oxidation of purpurogallin is improved considerably by employing hydrogen peroxide, and the acid (II; R = R′ = R″ = H), obtained in 30% yield, has therefore been made readily accessible for further investigation.



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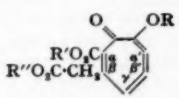

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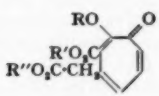


(III.)

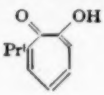
(IV.)

Several relatively simple tropolone derivatives have been isolated from natural sources. In 1936, Nozoe (*Bull. Chem. Soc., Japan*, 1936, **11**, 295) reported the isolation of hinokitiol from the acid portion of the essential oil of *Chamaecyparis taiwanensis*, and later studies (Iinuma, *J. Chem. Soc., Japan*, 1943, **64**, 742; Nozoe and Katsura, *J. Pharm. Soc., Japan*, 1944, **64**, 181,

* The structure (II; R = R′ = R″ = H) and the tautomeric 2-carboxy-3-hydroxy-4-keto*cyclo*heptatrienylacetic acid structure (III; R = R′ = R″ = H) are regarded as equivalent and the dual nature of all hydroxy*cyclo*heptatrienones (tropolones) is implied throughout this communication. The α, β, γ enumeration of the tropolone positions, as in (II), will in general be used. Ethers corresponding to (II) and (III) (or *vice versa*) have been isolated in several cases (p. 563) and here we ascribe a suffix-A to the higher-melting and less soluble ether, and a suffix-B to its isomer, until the structures can be determined.

and unpublished results *) indicate the identity of hinokitiol and β-thujaplicin (IV; R = H, R′ = Pr^{i}) isolated together with the α- (VI) and γ- (VII) isomers from the heartwood of red cedar (*Thuja plicata* Don.) by Erdtman and his co-workers (*Nature*, 1948, **161**, 719; *Acta Chem. Scand.*, 1948, **2**, 625, 639, 644). As originally suggested by Dewar (*loc. cit.*, pp. 50, 479), puberulic and stipitatic acids, isolated by Raistrick and his co-workers (*Biochem. J.*, 1932, **26**, 441; 1942, **36**, 242) from the culture media of *Penicillium puberulum* and *P. stipitatum* respectively, have been shown to be the tropolones (VIII; R = OH) and (VIII; R = H) respectively (Corbett, Hassall, Johnson, and Todd, *J.*, 1950, 1; Corbett, Johnson, and Todd, *ibid.*, pp. 6, 147). In view of the increasing interest in the chemistry of these simple tropolones it appeared desirable to communicate the results of one of several investigations in progress which have (*a*) provided evidence in favour of structure (II; R = R′ = R″ = H) and (IV; R = H, R′ = Me), (*b*) illustrated the tautomerism of the ketol grouping and the stability of the tropolone ring system, and (*c*) led to the preparation of the parent 2-hydroxy*cyclo*heptatrienone (tropolone) (IV; R = R′ = H). These results were discussed during a lecture to the Bedson Club at King's College, Newcastle-on-Tyne, on March 10th, 1950, and also to the Chemical Society at St. Andrews on 7th April, 1950, and a brief account of the synthesis of tropolone has appeared in *Chem. and Ind.*, 1950, 441. Announcements of the preparation of tropolone (IV; R = R′ = H) have also been made by Cook, Gibb, Raphael, and Somerville (*Chem. and Ind.*, 1950, 427) and by Doering and Knox (*J. Amer. Chem. Soc.*, 1950, **72**, 2305).

(V.)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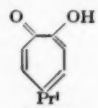
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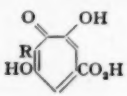
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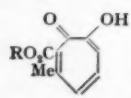

(IX.)

β-Methyltropolone (IV; R = H, R′ = Me) is a weak acid, dissolving slowly in aqueous sodium hydrogen carbonate to give a yellow solution from which the tropolone may be partly recovered by ether. Addition of lead acetate to an aqueous solution of β-methyltropolone gave an insoluble lead complex, and the copper salt, likewise precipitated from aqueous solution, crystallised from chloroform. β-Methyltropolone and its derivative (II; R = R′ = R″ = H) had no ketonic properties, and in this respect, as well as in their positive ferric tests, they closely resembled the thujaplicins (Erdtman *et al.*, *locc. cit.*), and stipitatic, puberulic, and puberulonic acids (Corbett *et al.*, *locc. cit.*). Fusion of β-methyltropolone with potassium hydroxide resulted in the production of *m*-toluic acid. The yield was not high and, although similar benzilic acid changes occur with other tropolones, it should be noted that structural factors play an important part. The change appears to occur with great ease in the colchicine–*allo*colchicine transformation (Lettré, *Angew. Chem.*, 1947, **59**, A, 218; Šantavý, *Helv. Chim. Acta*, 1948, **31**, 821; Fernholz, *Annalen*, 1950, **568**, 63), becomes more difficult with purpurogallin (*J.*, 1949, 3271), stipitatic acid, and γ-thujaplicin, and has not been observed with α- and β-thujaplicins (Erdtman *et al.*, *locc. cit.*) or puberulic acid (Corbett *et al.*, *locc. cit.*); on the other hand Nozoe (*loc. cit.*) reports that dinitrohinokitiol (dinitro-β-thujaplicin) is converted by merely warming it with water into a dinitro*iso*propylbenzoic acid.

As in the cases of purpurogallin and its methyl ethers, the catalytic reduction of β-methyltropolone was very sensitive to modifications in the quality of the catalyst. For an acetic acid solution in the presence of platinic oxide, the hydrogen uptake corresponded to 3·5 molecular proportions, and the oily product, unlike the starting material, was a non-acidic mixture containing some ketonic material which gave an amorphous 2 : 4-dinitrophenylhydrazone. The oil, probably a mixture of *cyclo*heptanediols and hydroxy*cyclo*heptanones, consumed approximately one molecular proportion of periodic acid, and yielded 4-methylnonanedial which was isolated as the bis-2 : 4-dinitrophenylhydrazone. Further oxidation of the oily dialdehyde with potassium permanganate gave β-methylpimelic acid which was identified by comparison of the acid, m. p. 45—48°, the anilide, m. p. 137° (Einhorn and Ehret, *Annalen*, 1897, **295**, 180, 80), and the *S*-benzylthiuronium salt, m. p. 172—173°, with specimens prepared from 3-methyl*cyclo*hexanone by methods based on those employed (*a*) by Kötz and Hesse (*Annalen*, 1905, **342**, 314) and (*b*) for the conversion of *cyclo*hexanone into pimelic acid. Condensation of 3-methyl*cyclo*hexanone with ethyl oxalate gave ethyl 2-keto-4-methyl*cyclo*hexylglyoxylate, which when heated yielded ethyl 2-keto-4-methyl*cyclo*hexanecarboxylate, and alkaline hydrolysis of the last gave β-methylpimelic acid.

* Most of the work was done at Taikoku Imperial University, Formosa, between 1940 and 1948.

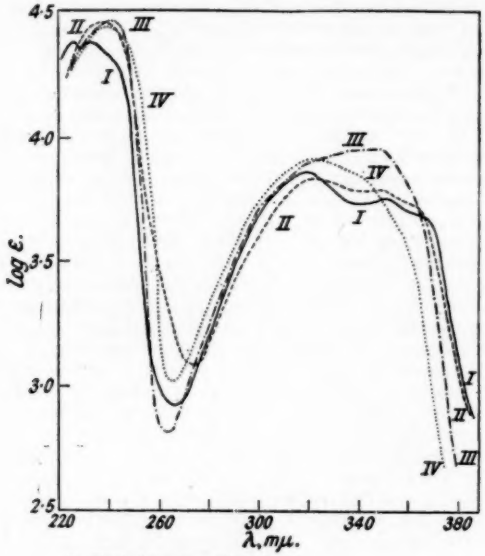
The conversion of β-methyltropolone into β-methylpimelic acid provides conclusive evidence for structure (IV; R = H, R′ = Me) or its tautomeric modification. The existence of such tautomerism in the tropolones is supported by the isolation of isomeric diacetyl and trimethyl derivatives of stipitatic acid (Raistrick *et al.*, *locc. cit.*), the formation of two readily hydrolysable *O*-methyl ethers, *viz.*, colchicine and *iso*colchicine, by methylation of colchiceine (Johanny and Zeisel, *Monatsh.*, 1888, **9**, 873; Lettré and Fernholz, *J. physiol. Chem.*, 1943, **273**, 175; Meyer and Reichstein, *Pharm. Acta Helv.*, 1944, **19**, 127; Sorkin, *Helv. Chim. Acta*, 1946, **29**, 246), and further examples have been encountered in the present investigation. Methylation of α-carboxy-β-carboxymethyltropolone (II; R = R′ = R″ = H) with diazomethane gave two isomeric trimethyl derivatives, -A, m. p. 110°, and -B, m. p. 73°, which are (II; R = R′ = R″ = Me) and (III; R = R′ = R″ = Me) or *vice versa*; the ether-A has been reported previously (*J.*, 1948, 1045). Methylation of (II; R = R′ = R″ = H) with methyl sulphate in alkaline solution gave a compound, which is regarded as the dimethyl ester α-carbomethoxy-β-carbomethoxymethyltropolone (II; R = H, R′ = R″ = Me) on account of its positive ferric reaction. Hydrolysis of the isomeric trimethyl derivatives and of the dimethyl ester took place very readily with cold sodium hydroxide solution and yielded in all cases the same dibasic acid, which gave a positive ferric test and must be either α-carbomethoxy-β-carboxymethyl- (II; R = R″ = H, R′ = Me) or α-carboxy-β-carbomethoxymethyl-tropolone (II; R = R′ = H, R″ = Me). The latter structure is however very improbable as the mild hydrolytic conditions are unlikely to affect the tertiary 2-carbomethoxy-group, but we failed to obtain experimental evidence by reaction with phenylmagnesium bromide as unrecognisable products were produced. The acid ester (II; R = R″ = H, R′ = Me) did not condense with piperonaldehyde, and was recovered after prolonged treatment with selenium dioxide, but it readily lost carbon dioxide at the melting point. The resulting α-carbomethoxy-β-methyltropolone (IX; R = Me) was soluble in sodium hydrogen carbonate solution, gave a positive ferric test, and was converted by prolonged boiling with 20% potassium hydroxide solution into α-carboxy-β-methyltropolone (IX; R = H) which yielded β-methyltropolone (IV; R = H, R′ = Me) on decarboxylation.

Two isomeric *p*-nitrobenzyl ethers (-A, m. p. 172°; -B, m. p. 160°) of β-methyltropolone have been prepared; on hydrolysis, both were reconverted into β-methyltropolone. In the same way methylation with diazomethane gave a mixture of β-methyltropolone methyl ether-A, m. p. 97°, and -B, m. p. 46°, which were separated by fractional crystallisation of their picrates. Both ethers gave β-methyltropolone on hydrolysis with alkali, but they showed remarkable differences in behaviour towards selenium dioxide in boiling dioxan. The low-melting methyl ether-B, which is markedly hygroscopic, was converted into a mixture of β-formyltropolone methyl ether-B (IV; R = Me, R′ = CHO, or its isomer) and a small amount of β-carboxytropolone methyl ether-B, but the higher-melting methyl ether-A was oxidised much more slowly and underwent simultaneous hydrolysis with the production of β-formyltropolone. The more rapid oxidation of the methyl ether-B may be indicative of a shorter conjugated system between the carbonyl and the methyl group, but, although this may be used as an argument in favour of structure (IV; R = R′ = Me), we prefer to regard the assignment of formulæ to the tautomeric forms as arbitrary at the present time. Further oxidation with sodium hydroxide and silver oxide (cf. Pearl, *J. Amer. Chem. Soc.*, 1946, **68**, 429) converted β-formyltropolone methyl ether-B in goods yields into β-carboxytropolone (IV; R = H, R′ = CO_2H), which was also obtained by alkaline hydrolysis of β-carboxytropolone methyl ether-B. The aldehydes (IV; R = H, R′ = CHO) and (IV; R = Me, R′ = CHO), and the corresponding acids, offer numerous synthetical possibilities which are under investigation. β-Carboxytropolone has been decarboxylated with copper powder in boiling quinoline, to give the parent tropolone (IV; R = R′ = H), m. p. 50°, which dissolves slowly in aqueous sodium hydrogen carbonate to give a yellow solution, gives with neutral ferric chloride a dark red colour which becomes green on dilution or acidification, yields a characteristic copper salt, and is devoid of ketonic properties.

Although no systematic study of the substitution reactions of the tropolones has been reported, it is evident from a number of observations that considerable aromaticity is displayed. Thus Raistrick (*Biochem. J.*, 1942, **36**, 242) showed that stipitatic acid was substituted by bromination in 80% acetic acid solution, and Nozoe (*locc. cit.*) mentions several mono-, di-, and tri-halogen and -nitro-substitution products of hinokitiol. We have observed that β-methyltropolone reacts with bromine in chloroform to give a red complex which is readily decomposed by water, yielding a difficultly separable mixture of mono- and di-bromo-substitution products. Although the structures of these derivatives have not been established, largely because of failure to achieve the benzilic acid transformation with them, the stability towards aqueous or alcoholic potassium hydroxide suggests that substitution has occurred in the tropolone nucleus and not in

the methyl group. It is probable that substitution occurs in a position activated by the hydroxyl group, particularly as the tropolones will condense with diazonium compounds in alkaline solution. Diazotised aniline gave red precipitates with alkaline solutions of tropolone or the β-methyl derivative, and the latter gave a crystalline red azo-dye, $C_{15}H_{14}O_2N_2$, m. p. 177—178° (decomp.), with diazotised *p*-toluidine. This azo-dye has been reduced by sodium dithionite (hydrosulphite) to a yellow aminotropolone, m. p. 224°, which was converted into a hydroxytropolone, m. p. 232—233° (decomp.), by the action of nitrous acid. Further investigations of the amino- and hydroxy-compound are in progress.

The lack of ethylenic and ketonic properties, and the weak acidic properties of the tropolones are understandable on the basis of their structure in which the carbonyl and hydroxyl groups, separated by a triene system, may be considered to be a trivinyl analogue of a carboxylic acid. The ready hydrolysis of the tropolone ethers (see pp. 566, 568) is also explicable by their constitutional resemblance with the ester of a carboxylic acid. It is probable however, that a detailed elucidation of the structure of the tropolone ring system must await further physical measurements.



I. Tropolone in methanol.
II. β-Methyltropolone in methanol.
III. β-Methyltropolone methyl ether-B in methanol.
IV. β-Methyltropolone methyl ether-A in methanol.

Mr. H. J. V. Tyrrell and Mr. O. S. Mills have shown that in *cyclo*hexane and benzene solutions, β-methyltropolone (IV; R = H, R′ = Me) is not associated at concentrations at which carboxylic acids are almost completely dimerised. Nozoe (*locc. cit.*) suggested that the relatively high boiling point of hinokitiol was indicative of a bimolecular structure, but our molecular weight determinations do not support this view. On the other hand they indicate a considerable degree of intramolecular hydrogen bonding of some type.

The ultra-violet absorption spectra of a number of tropolone derivatives have been measured, and the results, shown in the figure, resemble closely those, reported during the course of our work, for the thujaplicins (Erdtman *et al.*, *locc. cit.*), and stipitatic, puberulic, and puberulonic acids (Corbett *et al.*, *locc. cit.*). The results quoted by Cook, Gibb, Raphael, and Somerville (*loc. cit.*) are in close agreement with our observations. Those of Doering and Knox (*loc. cit.*) show some discrepancies (their solvent is not stated).

The ultra-violet spectra indicate the general aromatic nature of the tropolone ring; the shift of the spectrum of the methyl ethers to shorter wave-length relative to the tropolone band and the disappearance of the vibrational structure in the longer-wave absorption of the methyl

ether show marked similarity with the results of Morton and Earlam (*J.*, 1941, 159) on 1-hydroxy- and 1-methoxy-anthraquinones and suggest some type of internal hydrogen bonding.

Tarbell and his co-workers (*J. Amer. Chem. Soc.*, 1950, **72**, 240, 243, 379) have examined the infra-red absorption of γ-thujaplicin and β-methyltropolone and interpret the results as indicating a large shift in the carbonyl stretching frequency on account of conjugation but they fail to detect internal hydrogen bonding. We are greatly indebted to Mrs. Broomfield, Imperial Chemical Industries Limited, Billingham Division, for the following report on the infra-red spectra of four tropolone derivatives. " The spectra of four tropolones were recorded in chloroform solution over the region of 6—7 μ. (1300—1700 cm.$^{-1}$), and the following maxima were observed :

Tropolone	1300	1437	1474	1550	1610
β-Methyltropolone *	1396	1450	1474	1542	1610
β-Methyltropolone methyl ether-A	1474	1508	1560—70	1600	1630
β-Methyltropolone methyl ether-B	1474	1498	1560—70	1605	1630

* These values agree with those cited by Scott and Tarbell (*loc. cit.*).

" The infra-red absorption bands are not easy to assign to specific bonds or groups in the tropolone ring. The band in the 1610-cm.$^{-1}$ region for β-methyltropolone was assigned by Scott and Tarbell (*loc. cit.*) to the carbonyl stretching vibration, which is known to occur at much lowered frequency when involved in a highly conjugated system. It is interesting to note that in the parent tropolone this band occurs in exactly the same position, while a somewhat different picture is presented by the two isomeric monomethyl ethers, apparently indicating some effect of the proximity of the hydroxyl on the carbonyl group. The hydroxyl group in tropolone and β-methyltropolone is characterised by a weak broad band around 3200 cm.$^{-1}$, which, since a completely free hydroxyl group is known to give a band above 3500 cm.$^{-1}$, would almost certainly indicate some type of internal hydrogen bonding. It is doubtful if " zwitterionisation " would lead to such a markedly low hydroxyl frequency."

The isolation of tautomeric forms of the ethers of unsymmetrical tropolones (p. 563), but the non-existence of more than one form of β-methyltropolone, are also probably best interpreted at the present time by internal hydrogen bonding.

Some preliminary measurements made by Mr. Mills and Mr. Tyrrell have shown that β-methyltropolone and the methyl ether-A have dipole moments in benzene solution of 3·9 and 4·9 D. respectively. This greater value for the methyl ether indicates a considerable contribution from polar structures, which also accounts for the increased water solubility of the tropolone methyl ethers. These dipole moment measurements are being continued, but it is difficult to devise a satisfactory explanation for the high dipole moment of β-methyltropolone itself.

Antibiotic tests have been carried out with several tropolone derivatives by Dr. Elsden and Mr. Marshall of the Bacteriology Department, Sheffield University, who find that in Fleming's medium β-methyltropolone inhibits the growth of *Staph. aureus* at dilutions of 1 : 160,000, and of *B. coli* at 1 : 20,000, but that other derivatives are less active. These and other biological results will be described more fully later.

Experimental.

Purpurogallin, prepared in 60—70% yield by oxidation of pyrogallol with potassium iodate (Evans and Dehn, *J. Amer. Chem. Soc.*, 1930, **52**, 3647), was purified by vacuum sublimation or by crystallisation from anisole; red prisms, m. p. 276° (decomp.), were obtained.

2-Carboxy-4-hydroxy-3-ketocycloheptatrienylacetic Acid (*α-Carboxy-β-carboxymethyltropolone*) (II; R = R′ = R″ = H).—Hydrogen peroxide (25 c.c.; 100-vol.) was added dropwise with stirring to a solution of purpurogallin (10 g.) in 23% potassium hydroxide solution (650 g.) which was preheated to 90—95°. After cooling of the mixture, sodium hydrogen sulphite (5 g.) was added, and the clear deep-red solution was acidified by addition of 40% sulphuric acid (270 c.c.). The deposited potassium sulphate was collected and the filtrate extracted continuously with ether for 40 hours. After being dried, the red extract yielded a dark brown oil from which the acid (II; R = R′ = R″ = H) slowly separated as yellow crystals (2·5—3 g.). After these had been washed with a little ether and crystallised from glacial acetic acid, colourless prisms, m. p. 183—184° (decomp.) (rapid heating) (Part I, *loc. cit.*), were obtained.

An attempt to oxidise the acid in boiling aqueous solution with selenium dioxide gave much tar and a small amount of yellow amorphous solid, gradually darkening between 170° and 190° and yielding with Brady's reagent a red precipitate which was not purified.

Methylation of α-Carboxy-β-carboxymethyltropolone.—Diazomethane (1·5 g.) in ether (50 c.c.) was added slowly to a solution of the acid (2·24 g.) in acetone (50 c.c.). After 16 hours, evaporation of the

solvent left a brown oil (2·7 g.) which deposited crystals of α-carbomethoxy-β-carbomethoxymethyltropolone methyl ether-A; recrystallisation from benzene yielded colourless prisms (1·2 g.), m. p. 110°, described previously in Part I (*loc. cit.*). Evaporation of the ethereal mother-liquors gave a pale yellow oil (1·4 g.), which eventually solidified and was repeatedly extracted with light petroleum (b. p. 40—60°). On cooling, the concentrated extract deposited the *dimethyl ester methyl ether-B*, which crystallised from benzene–light petroleum (b. p. 40—60°) in colourless prisms, m. p. 72—73° (Found: C, 58·9; H, 5·3. $C_{13}H_{14}O_6$ requires C, 58·7; H, 5·3%). The isomeric ethers were mixed separately with methyl oxalate in dioxan in presence of potassium methoxide; small yields were obtained of an amorphous yellow acid which could not be purified.

α-Carbomethoxy-β-carboxymethyltropolone (II; R = R″ = H; R′ = Me).—Each of the isomeric ethers-A and -B was quantitatively hydrolysed with cold 2N-sodium hydroxide (5 vols.) to *α-carbomethoxy-β-carboxymethyltropolone* (II; R = R″ = H; R′ = Me), which separated from methyl alcohol or water in colourless elongated plates, m. p. 179—180° (decomp.) (rapid heating) (Found: C, 55·5; H, 4·2. $C_{11}H_{10}O_6$ requires C, 55·5; H, 4·2%), soluble in sodium hydrogen carbonate solution with effervescence and giving a red colour with neutral ferric chloride solution, becoming green on dilution or acidification.

α-Carbomethoxy-β-methyltropolone (IX; R = Me).—The acid (II; R = R″ = H; R′ = Me) described above was decarboxylated by heating it at 180°, and the product, purified first by sublimation and then by crystallisation from *cyclo*hexane, was obtained as colourless prisms, m. p. 122—123° (Found: C, 61·8; H, 5·2. $C_{10}H_{10}O_4$ requires C, 61·9; H, 5·2%), which were slightly soluble in sodium hydrogen carbonate solution and gave a deep red colour with ferric chloride. The *ester* was not oxidised when heated with selenium dioxide in aqueous solution for 18 hours, and could not be condensed with piperonaldehyde in presence of sodium hydroxide. A complex reaction took place when the ester was mixed with excess of phenylmagnesium bromide: the neutral product was precipitated by addition of light petroleum (b. p. 40—60°) to its ethereal solution as a light brown amorphous solid, which gave a negative ferric test but was not further investigated.

α-Carboxy-β-methyltropolone (IX; R = H).—The ester (IX; R = Me) (0·2 g.) described above was refluxed with a solution of potassium hydroxide (1·25 g.) in water (2 c.c.) and methyl alcohol (3 c.c.) for 6 hours. The cooled solution was acidified with hydrochloric acid, and the product, isolated with ether, was taken up in sodium hydrogen carbonate solution, recovered, and extracted with ether. Evaporation of the dried extract gave *α-carboxy-β-methyltropolone* (IX; R = H) (0·15 g.); crystallisation from acetone–light petroleum (b. p. 40—60°) gave colourless prisms, m. p. 186—187° (decomp.) (Found: C, 60·0; H, 4·8. $C_9H_8O_4$ requires C, 60·0; H, 4·5%), which gave a ferric test and was decarboxylated to β-methyltropolone, m. p. 76—77°, by heating it at 190°.

α-Carbomethoxy-β-carbomethoxymethyltropolone.—Methyl sulphate (8·4 c.c.) was added to α-carboxy-β-carboxymethyltropolone (6 g.) dissolved in a solution of sodium hydroxide (3·3 g.) in water (15 c.c.). After 30 hours' shaking the light brown precipitate of *α-carbomethoxy-β-carbomethoxymethyltropolone* (II; R = H; R′ = R″ = Me) (5·5 g.) was collected and crystallised from benzene; colourless prisms, m. p. 107° (Found: C, 57·2; H, 4·9. $C_{12}H_{12}O_6$ requires C, 57·1; H, 4·8%), were obtained, which gave a deep red ferric test, dissolved slowly in sodium hydrogen carbonate solution, and underwent rapid hydrolysis to α-carbomethoxy-β-carboxymethyltropolone, m. p. 179—180° (decomp.), with cold sodium hydroxide solution.

β-Methyltropolone (IV; R = H; R′ = Me), prepared by heating α-carboxy-β-carboxymethyltropolone to its m. p., and purified by sublimation, crystallised from light petroleum (b. p. 40—60°) in colourless prisms, m. p. 76—77° (see Part I, *loc. cit.*). The *copper* salt, precipitated by addition of copper acetate to an aqueous solution of (IV; R = H; R′ = Me), separated from concentrated chloroform solution in green prisms containing solvent of crystallisation which was eliminated slowly in the air, or in 1 hour at 100°; the salt had m. p. 280—282° (decomp.) (Found: C, 57·6; H, 4·4. $C_{16}H_{14}O_4Cu$ requires C, 57·6; H, 4·2%). β-Methyltropolone was recovered after being heated with an aqueous solution of selenium dioxide for 2 hours at 160°, and it did not react with piperonaldehyde in a warm alcoholic solution of potassium ethoxide.

Fusion of β-Methyltropolone with Potassium Hydroxide [with Dr. P. L. Pauson].—The methyltropolone (0·1 g.) was gradually heated to 300° with potassium hydroxide (2 g.) and water (0·5 c.c.), and the mixture was maintained at 300° for 10 minutes. Acidification yielded *m*-toluic acid, which after purification by steam distillation, sublimation, and crystallisation from water had m. p. 110—111°, undepressed by admixture with an authentic specimen. Identification was confirmed by preparation of the *S*-benzylthiuronium salt, which separated from alcohol in needles, m. p. 174° (Found: N, 9·4. Calc. for $C_{16}H_{18}O_2N_2S$: N, 9·3%) (Donleavy, *J. Amer. Chem. Soc.*, 1936, **58**, 1004, gives m. p. 164°), and by conversion in benzene solution into the *benzylammonium* salt, which separated from benzene in colourless needles, m. p. 145—147° (Found: N, 5·9. $C_{15}H_{17}O_2N$ requires N, 5·8%).

Conversion of β-Methyltropolone into β-Methylpimelic Acid.—β-Methyltropolone (0·4 g.) was reduced in glacial acetic acid (15 c.c.) in the presence of freshly prepared platinic oxide (0·02 g.); hydrogen (250 c.c., 3·5 moles) was absorbed during 3 hours, reduction then being complete. Removal of the solvent yielded a neutral amber oil (0·4 g.) which gave an amorphous 2 : 4-dinitrophenylhydrazone. A solution of the neutral reduction product (0·4 g.) in water (25 c.c.) reacted with 0·25M-periodic acid (13 c.c., 1 mole), and the product, isolated with ether, was an oil (0·4 g.) which partly dissolved in sodium hydrogen carbonate solution. The neutral fraction, containing β-methylpimelic dialdehyde, gave a *bis*-2 : 4-*dinitrophenylhydrazone*, which separated from alcohol as an amorphous orange powder, m. p. 155—165° (decomp.) (Found: C, 48·4; H, 4·4; N, 22·0. $C_{20}H_{22}O_8N_8$ requires C, 47·9; H, 4·4; N, 22·3%). The combined neutral and acidic fractions (0·4 g.) were oxidised with 3% potassium permanganate solution (12 c.c.) in cold 10% sodium carbonate solution. After half an hour the liquid

was saturated with sulphur dioxide, and extracted with ether. The dried extract yielded a colourless acidic oil (0·3 g.) which gradually solidified, having m. p. 45—48° undepressed on admixture with authentic β-methylpimelic acid (Einhorn and Ehret, *loc. cit.*, give m. p. 48°). The anilide, prepared by refluxing the acid with aniline for 20 hours, crystallised from aqueous alcohol in colourless needles, m. p. 134° (Einhorn and Ehret, *loc. cit.*, give m. p. 137°) undepressed on admixture with an authentic specimen. The *S-benzylthiuronium* salt, precipitated by adding a slight excess of a 15% solution of *S*-benzylthiuronium chloride in alcohol to an aqueous solution of the acid, crystallised from aqueous alcohol in white needles, m. p. 172—173° (decomp.) (Found : C, 57·0; H, 6·7; N, 10·7. $C_{24}H_{34}O_4N_4S_2$ requires C, 56·9; H, 6·7; N, 11·1%), identical with a specimen prepared from synthetic β-methylpimelic acid.

Synthesis of β-Methylpimelic Acid.—An ice-cold mixture of 3-methyl*cyclo*hexanone (45 g.) and ethyl oxalate (58·4 g.) was added during 20 minutes to a well-stirred solution of sodium ethoxide (from sodium, 9·2 g.) in absolute alcohol (120 c.c.) cooled below 10°. The cloudy orange-yellow solution was stirred for 1 hour at $<10°$ and a thick yellow precipitate gradually separated. After a further 4 hours' stirring at room temperature, a mixture of concentrated sulphuric acid (11 c.c.) and ice (100 g.) was added, and the precipitated yellow oil was taken up in ether and washed with water. Unchanged ester and ketone were removed by distillation, and crude ethyl 2-keto-4-methyl*cyclo*hexylglyoxylate (40 g.) was collected at 120—150°/12 mm. This crude ester (40 g.) was heated in an oil-bath at 170°/40 mm. with powdered glass (2 g.) and a trace of iron powder. Slow distillation during 1 hour yielded ethyl 2-keto-4-methyl*cyclo*hexanecarboxylate (32 g.), b. p. 135—148°/40 mm. (Kotz and Hesse, *loc. cit.*, give b. p. 146°/40 mm.), which was added during 1 hour to a well-stirred solution of sodium hydroxide (30 g.) in dry methyl alcohol (90 c.c.) in an oil-bath at 120°. After a further hour, the mixture was diluted with water (150 c.c.), and the methyl alcohol removed. Concentrated sulphuric acid (42 c.c.) was added to the cooled solution which was clarified with charcoal and extracted with ether for 10 hours. The dried extract yielded β-methylpimelic acid (14 g.) as a colourless oil which gradually solidified and was purified by distillation at 215°/10mm., giving a colourless crystalline distillate, which had m. p. 45—48° after remaining in contact with a porous tile for some time. The anilide, m. p. 137°, and *S*-benzylthiuronium salt, m. p. 172—173° (decomp.), were prepared as described above.

Bromination of β-Methyltropolone.—Bromine (2·4 g.) in chloroform (10 c.c.) was added dropwise with stirring to a solution of β-methyltropolone (2·0 g.) in chloroform (10 c.c.); an orange-red solid rapidly separated. The mixture was shaken with water (20 c.c.), the yellow chloroform layer was removed, and the aqueous layer extracted with chloroform. The combined and dried extracts gave a yellow oil (3 g.) which slowly solidified and yielded by fractional crystallisation from light petroleum (b. p. 40—60°) a small quantity of *dibromo*-derivative as cream coloured prisms, m. p. 139—140° (Found : C, 32·7; H, 2·2. $C_8H_6O_2Br_2$ requires C, 32·7; H, 2·1%), and a more soluble *monobromo*-compound (1 g.) as colourless prisms, m. p. 85—86° (Found : C, 44·7; H, 3·3. $C_8H_7O_2Br$ requires C, 44·7; H, 3·3%). This monobromo-derivative was recovered after being heated with potassium hydroxide (4 parts by wt.) in water (10 vols.) and ethyl alcohol (10 vols.) for 4 hours. Fusion with potassium hydroxide (10 parts by wt.) at 260° for half an hour gave a small amount of acidic material which did not give a ferric test, but the yield was insufficient for purification and identification.

Reaction of Toluene-p-diazonium Chloride with β-Methyltropolone.—*p*-Toluidine (0·4 g.) in N-hydrochloric acid (10 c.c.) was diazotised by addition of sodium nitrite (0·26 g.) in water (2 c.c.), and the solution was poured with stirring into a solution of β-methyltropolone (0·5 g.) in 2N-sodium hydroxide (10 c.c.) and water (35 c.c.). The bright red solid was collected, suspended in water, acidified with dilute hydrochloric acid and the orange-red *azo*-compound crystallised from ethyl alcohol, giving small flat needles, m. p. 177—178° (decomp.) (Found : C, 70·4; H, 5·8; N, 10·9. $C_{15}H_{14}O_2N_2$ requires C, 70·9; H, 5·5; N, 11·0%).

(?-)*Amino-β-methyltropolone.*—A 10% solution of sodium dithionite (*ca.* 100 c.c.) was added to a warm suspension of the above azo-compound (3·0 g.) in acetone (200 c.c.) and water (100 c.c.). The deep-yellow solution was made alkaline by the addition of 2N-sodium hydroxide (10 c.c.) and, after removal of the acetone by distillation, the *p*-toluidine was taken up in benzene. The aqueous solution was made acid to litmus with dilute hydrochloric acid, neutralised with aqueous ammonia, and made faintly acid with acetic acid. Extraction with several portions of ethyl methyl ketone, and subsequent evaporation of the solvent yielded (?-)*amino-β-methyltropolone* (1·0 g.) which, purified by sublimation at 220°/0·5 mm., and crystallisation from ethanol, formed yellow prisms, m. p. 224° (decomp.) (Found : C, 63·4; H, 5·8; N, 9·5. $C_8H_9O_2N$ requires C, 63·6; N, 6·0; N, 9·3%), giving an intense reddish-violet colour with ferric chloride solution. The amine dissolved in dilute alkali, to give a deep-yellow solution, and dissolved in dilute hydrochloric acid to give a pale yellow solution, from which the hydrochloride separated as pale yellow needles, m. p. 205° (decomp.).

(?-)*Hydroxy-β-methyltropolone.*—A solution of sodium nitrite (0·68 g.) in water (5 c.c.) was added dropwise, with stirring, to a solution of the above amino-compound (1·5 g.) in 3N-sulphuric acid (10 c.c.) cooled to 10°. The diazo-compound was decomposed by heating the solution on a water-bath until there was no further evolution of nitrogen, and extraction with ether yielded a crystalline solid (0·4 g.), which was purified by sublimation at 220°/0·1 mm. and crystallisation from water. Cream coloured plates, m. p. 232—233° (decomp.), of (?-)*hydroxy-β-methyltropolone* (Found : C, 63·3; H, 5·3. $C_8H_8O_3$ requires C, 63·2; H, 5·3%) were obtained, giving an intense green colour with ferric chloride solution, and soluble in sodium hydrogen carbonate to give a yellow solution.

Ethers of β-Methyltropolone.—(a) *Methyl ethers.* β-Methyltropolone (3 g.) in ether (40 c.c.) was allowed to react for 20 hours with diazomethane (1·1 g.) in ether (100 c.c.); removal of the solvent gave a yellow oil (3·3 g.), which was dissolved in methanol (10 c.c.) and warmed with a solution of picric acid (5·3 g.) in methanol (10 c.c.). After cooling, the yellow crystalline solid was collected, and fractional crystallisation

from methanol yielded *β-methyltropolone methyl ether-B picrate* as yellow prisms, m. p. 130—131° (decomp.) (Found: C, 47·7; H, 3·4; N, 11·1. $C_{15}H_{13}O_9N_3$ requires C, 47·5; H, 3·5; N, 11·3%), and the *isomer-A picrate* as yellow needles, m. p. 160° (decomp.) (Found: C, 47·3; H, 3·7; N, 10·9%). The picrates were decomposed by extracting their chloroform solutions with sodium hydrogen carbonate solution, remaining impurities being removed by passage through an alumina column. Evaporation of the solutions yielded *β-methyltropolone methyl ether-B*, giving on distillation at 114°/0·1 mm. a white crystalline solid, m. p. 46° (Found: C, 71·7; H, 6·8. $C_9H_{10}O_2$ requires C, 72·0; H, 6·7%), and the isomeric *ether-A*, giving on crystallisation from light petroleum (b. p. 60—80°) colourless elongated plates, m. p. 96—97° (Found: C, 71·9; H, 6·5%). The low-melting ether rapidly absorbed moisture and became liquid on exposure to the atmosphere.

Both methyl ethers were water-soluble, gave a negative ferric test, and showed no ketonic reactions. They were quantitatively converted into β-methyltropolone, m. p. 76°, by being warmed for 5 minutes with 2N-sodium hydroxide (10 vols.).

(b) p-*Nitrobenzyl ethers.* β-Methyltropolone (2 g.) in 2% sodium hydroxide solution (28 c.c.) was mixed with a solution of *p*-nitrobenzyl bromide (3·2 g.) in ethyl alcohol (25 c.c.), and the mixture was refluxed for 2 hours. Fractional crystallisation of the product from alcohol gave *β-methyltropolone* p-*nitrobenzyl ether-A*, m. p. 172° (Found: C, 66·5; H, 4·7; N, 5·3. $C_{15}H_{13}O_4N$ requires C, 66·4; H, 4·8; N, 5·2%), and the more soluble p-*nitrobenzyl ether-B*, which separated in colourless needles, m. p. 160° (Found: C, 66·2; H, 4·7; N, 5·2%).

Either ether (0·1 g.) in alcohol (3 c.c.) was added to sodium hydroxide (0·4 g.) in water (2 c.c.), and the mixture was warmed in a water-bath for 10 minutes. The deep-red solution was acidified with dilute hydrochloric acid and extracted with ether. The extract was shaken with sodium hydroxide solution, the alkaline layer was acidified, and recovery with ether yielded β-methyltropolone, m. p. 74—76°, after sublimation and crystallisation from light petroleum (b. p. 40—60°).

Oxidation of β-Methyltropolone Methyl Ether-A.—The ether, m. p. 96—97° (1·6 g.), was refluxed with selenium dioxide (1·77 g.) in dioxan (25 c.c.) for 18 hours. The filtered solution was diluted with ether (100 c.c.), decanted from tar, and extracted with sodium hydrogen carbonate solution, and the extract well washed with ether. After acidification, continuous ether-extraction for 20 hours yielded a yellow crystalline solid (0·4 g.) which after several recrystallisations from water and sublimation at 150—160°/12 mm. gave *β-formyltropolone* as pale yellow needles, m. p. 159—160° (Found: C, 63·7; H, 4·0. $C_8H_6O_3$ requires C, 64·0; H, 4·0%). The neutral ether–dioxan liquors from the oxidation yielded a small amount of unchanged ether.

Oxidation of β-Methyltropolone Methyl Ether-B.—The ether, m. p. 46° (2·2 g.), was oxidised with selenium dioxide (2·5 g.) in dioxan (25 c.c.) for 8 hours, and separated into neutral and acidic products as described above. The neutral products gave *β-formyltropolone methyl ether-B* which crystallised from methyl alcohol or benzene in colourless needles (0·6 g.), m. p. 182—183° (Found: C, 65·8; H, 5·1. $C_9H_8O_3$ requires C, 65·8; H, 4·9%), giving a negative ferric test. The 2 : 4-*dinitrophenylhydrazone* separated from acetic anhydride in yellow needles, m. p. 292—295° (decomp.) (Found: C, 52·8; H, 3·5; N, 16·1. $C_{15}H_{12}O_6N_4$ requires C, 52·3; H, 3·5; N, 16·3%). The acidic product was crystallised several times from water; *β-carboxytropolone methyl ether-B* (0·4 g.) was obtained as pale yellow needles, m. p. 258° (Found: C, 60·0; H, 4·4. $C_9H_8O_4$ requires C, 60·0; H, 4·5%), which effervesced with sodium hydrogen carbonate solution, and gave no colour with ferric chloride. This acid was hydrolysed to β-carboxytropolone (see below), m. p. 217°, by warming it for a few minutes with dilute sodium hydroxide solution.

Oxidation of β-Formyltropolone or its Methyl Ether.—The free aldehyde or its ether (0·2 g.) was added to a suspension of freshly precipitated silver oxide (0·30 g.) in 4N-sodium hydroxide (2 c.c.) and warmed on the water-bath for half an hour. The cooled, filtered solution was acidified with dilute hydrochloric acid and extracted continuously with ether. Evaporation of the dried extract gave *β-carboxytropolone* (0·18 g.), which crystallised from dioxan in large prisms containing solvent of crystallisation. The solvent was removed when the substance was heated at 100° for half an hour; a crystalline powder, m. p. 217° (Found: C, 58·2; H, 3·9. $C_8H_6O_4$ requires C, 57·8; H, 3·6%), was obtained.

Decarboxylation of β-Carboxytropolone to Tropolone.—The acid (0·2 g.) was refluxed for 2 hours in quinoline (3 c.c.) in presence of copper bronze (50 mg.). The filtered and acidified solution was extracted with ether, and the tropolone was removed with dilute sodium hydroxide, recovered, and isolated with ether. The product rapidly solidified and crystallised from light petroleum (b. p. 40—60°) in colourless prisms (30 mg.), m. p. 49—50° (Found: C, 69·2; H, 5·1. Calc. for $C_7H_6O_2$: C, 68·9; H, 5·0%). Tropolone was very volatile and was readily lost on exposure to the atmosphere at ordinary temperature. It gave a deep red ferric test, becoming green on acidification, and a green copper salt which dissolved in chloroform, and it dissolved in sodium hydrogen carbonate to give a yellow solution.

Our thanks are offered to the Department of Scientific and Industrial Research for a maintenance grant to J. D. H., to the Imperial Chemical Industries Limited for a grant which defrayed some of the cost of the investigation, and to Dr. Elsden and Mr. Marshall for the results of the antibiotic tests.

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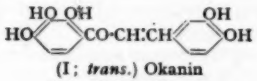
122. *The Chemistry of Extractives from Hardwoods. Part IV. Okanin and* iso*Okanin, the Isomeric* 2 : 3 : 4 : 3′ : 4′*-Pentahydroxychalkones.*

By F. E. King and T. J. King.

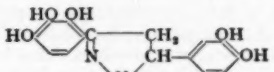
Two colouring matters, okanin and *iso*okanin, have been isolated from the yellowish-brown heartwood of the West African tree *Cylicodiscus gabunensis* Harms., okanin being identified as 2 : 3 : 4 : 3′ : 4′-pentahydroxychalkone by comparison with a synthetic specimen. The formation of distinct phenylhydrazones, converted on heating into a common pyrazoline, indicates that the two pigments are geometrical isomers.

Cylicodiscus gabunensis Harms., one of the largest trees in West Africa, is the source of a hard and dense wood known commercially as okan or African greenheart. A tendency to check and become distorted on seasoning renders it somewhat unsuitable for furniture manufacture, but owing to its high durability the timber is often used in its country of origin for heavy constructional work. In view of its classification as very resistant to decay, okan was included among a number of timbers of which extracts are now undergoing chemical examination. We are greatly indebted to Mr. W. O. Woodward, Director, The Nottingham Mills Co., for help in obtaining samples of okan.

The heartwood, which varies in colour from yellow to brown and is sometimes tinted green, is readily distinguished from the pinkish sapwood. A small-scale extraction of the heartwood gave only a negligible petroleum-soluble fraction, but the material (1·3%) removed by boiling ether appeared to be largely composed of the characteristic colouring matters of the timber, and a further quantity was found among the tannins which constitute the bulk of the considerable alcoholic extract (10—12%). These preliminary experiments enabled a simple procedure to be devised for the isolation of the pigments, consisting in boiling the powdered wood with alcohol and exhaustively extracting the resultant brown brittle resin with cold ether. The gummy ether-soluble portion hardened when stirred with water and was then readily fractionated by dissolving it in boiling 50% acetic acid. The portion crystallising when the solution was cooled amounted to 1·3% of the timber and was an orange compound, $C_{15}H_{12}O_6$, m. p. 235—240° (decomp.), which has been named okanin. By evaporation of the remaining solution and crystallisation of the solid residue from water, the yellow hydrated *iso*okanin, $C_{15}H_{12}O_6,1\frac{1}{2}H_2O$, m. p. 140° (efferv.), comprising approximately 1·8% of the wood, was obtained.



(I; *trans.*) Okanin
(II; *cis.*) *iso*Okanin



(III.)

Okanin dissolved in aqueous alkalis to deep-orange solutions from which it was recovered unchanged on acidification. It formed a deep red 2 : 4-dinitrophenylhydrazone typical of the αβ-unsaturated ketones and gave an intense ferric reaction and a purple colour on reduction with magnesium and alcoholic hydrogen chloride. These observations together with the molecular formula were suggestive of a pentahydroxychalkone structure, and it was then noticed that the melting point of okanin was similar to that of 2 : 3 : 4 : 3′ : 4′-pentahydroxychalkone (Russell and Todd, *J.*, 1934, 1506; Kurth, *J. Amer. Chem. Soc.*, 1939, **61**, 861). The identity of the two compounds appeared to be confirmed by the ultra-violet absorption of okanin which was in close agreement with the spectrum of the pentahydroxychalkone as determined by Russell, Todd, and Wilson (*J.*, 1934, 1940) but, whereas the pentabenzoate of the synthetic chalkone, its sole recorded derivative, is described as a solid, m. p. 85° (Russell and Todd, *loc. cit.*), the corresponding benzoate of okanin could not be obtained crystalline. However, a specimen of 2 : 3 : 4 : 3′ : 4′-pentahydroxychalkone which was then prepared from protocatechualdehyde and gallacetophenone by Kurth's method (*loc. cit.*) was indistinguishable from the natural compound, and their readily crystallisable penta-acetates were proved identical by the mixed melting point test.

The accompanying isomeric yellow pigment was found to be closely related to okanin, a solution of the former in dilute acid kept at 100° gradually depositing the less-soluble penta-

hydroxychalkone. Moreover, the derivative obtained from *iso*okanin and 2 : 4-dinitrophenylhydrazine in boiling 2N-hydrochloric acid was identical in its colour change at higher temperature and in decomposition point with okanin 2 : 4-dinitrophenylhydrazone. *iso*Okanin thus appeared to be the corresponding tetrahydroxyflavanone, but the acetylation of *iso*okanin to a penta-acetate which, moreover, was different from okanin penta-acetate, decisively excluded the possibility. It was thus evident that the two colouring matters were geometrical isomers, a conclusion strengthened by the quantitative formation of okanin when its isomer was heated above the melting point. The greater stability, higher melting point, etc., of okanin and its formation by synthesis all point to the *trans*-configuration (I) for this isomer, *iso*okanin therefore being the *cis*-modification (II). Instances of *cis–trans*-isomerism in the chalkone series have already been reported, *e.g.*, ω-benzylidene-4-*p*-tolylacetophenone (Badoche, *Bull. Soc. chim.*, 1928, **43**, 337) and α-bromo-β-methoxystyryl phenyl ketone (Dufraisse and Gillet, *Ann. Chim.*, 1929, **11**, 5), although the phenomenon is often confused with polymorphism (see Weygand and Hennig, *Ber.*, 1927, **60**, 2428), but we know of no previous example among the naturally-occurring chalkones.

An attempt was made to reduce the isomeric chalkones to the identical saturated ketone and thus obtain further proof of their *cis-trans*-relationship. Catalytic reduction of okanin resulted in the rapid absorption of one mole of hydrogen, and then slowly of a second, the reaction being interrupted without difficulty and the required ketone isolated as its 2 : 4-dinitrophenylhydrazone. *iso*Okanin, on the other hand, rapidly absorbed two moles of hydrogen at constant rate but, in presence of sodium hydroxide, the absorption was much slower and virtually ceased with the uptake of one mole, a 2 : 4-dinitrophenylhydrazone being obtained which was identical in appearance with that from dihydro-okanin. A comparison by the melting point method was unreliable, the two samples having indefinite decomposition points, but their identity was rigidly established by *X*-ray powder-diffraction photographs kindly prepared by Mr. S. C. Wallwork.

Catalytic reduction of the okanin and *iso*okanin penta-acetates also showed unexpected variation, the former rapidly consuming two moles of hydrogen, while absorption of the second equivalent by the *iso*okanin derivative occurred only very slowly.

The relationship of the two compounds was unambiguously established by a study of their phenylhydrazones. As with the 2 : 4-dinitrophenylhydrazones, the rates of reaction of the two isomeric chalkones with phenylhydrazine differed considerably. With okanin the reaction was extremely slow at room temperature, but was apparently complete after heating at 100°, although the product could not be obtained solid. *iso*Okanin, however, readily gave a crystalline phenylhydrazone at room temperature. Heating with acetic acid, a reagent known to cause ring-closure of chalkone phenylhydrazones to pyrazolines (cf. Raiford and Peterson, *J. Org. Chem.*, 1939, **1**, 524), resulted in the formation from both derivatives of the identical crystalline product, 5-(3 : 4-dihydroxyphenyl)-3-(2 : 3 : 4-trihydroxyphenyl)-1-phenyl-Δ^2-pyrazoline (III). This pyrazoline was also obtained when *iso*okanin phenylhydrazone was heated in ethanol, or from the reaction of the chalkone and phenylhydrazine on a steam-bath.

Experimental.

Okanin and iso*Okanin.*—Finely divided okan (200 g.) was twice heated in boiling ethanol (1·5 l.) for 5 hours and the filtered extracts were combined and evaporated to dryness on a steam-bath under reduced pressure. The chocolate-brown resin (27 g.) was readily broken up and removed from the flask, but it liquefied in contact with hot ether and was therefore triturated with small portions (50 c.c.) of the solvent in a mortar until the extracts were no longer coloured (total, 1 l.). The solution, after treatment with charcoal, was evaporated and thus gave a thick gummy residue, which on trituration with water (50 c.c.) solidified and was collected.

The crude product (8·0 g., 4%) was dissolved in boiling acetic acid (100 c.c. of 50%) from which the *okanin* separated in rosettes of bright orange crystals (2·6 g.) which when recrystallised from aqueous acetic acid or aqueous alcohol appeared as flat orange leaflets, m. p. 235—240° (decomp.) (Found, in an air-dried sample: C, 59·3; H, 4·7. $C_{15}H_{12}O_6,H_2O$ requires C, 58·8; H, 4·6. Found, after drying at 150°: C, 62·7; H, 4·2. $C_{15}H_{12}O_6$ requires C, 62·5; H, 4·2%). A specimen of the synthetic chalkone was identical in appearance and also had m. p. 235—240°. Russell and Todd (*loc. cit.*) give m. p. 233° (decomp.); Kurth (*loc. cit.*), m. p. 249°. The alcoholic ferric reaction of both specimens was chocolate-brown.

Evaporation of the mother-liquor from the first crystallisation of okanin left a yellow-brown residue which crystallised from water (100 c.c.; charcoal) as lemon-yellow needles (3·7 g.) of iso*okanin* sesquihydrate, m. p. 140° (efferv.) (Found, in an air-dried sample: C, 57·8; H, 4·7. $C_{15}H_{12}O_6,1\frac{1}{2}H_2O$ requires C, 57·2; H, 4·7%. Found, after drying at 120°: C, 62·2; H, 4·45%). The pure *iso*okanin was easily soluble in hot water and the ordinary organic solvents, and readily dissolved in alkali to an orange solution from which it was precipitated on acidification. The ferric chloride reaction in alcohol was

brownish-green. On digestion of a strong solution of the compound in 2% aqueous hydrochloric acid at 100° the liquid darkened and the less-soluble *trans*-pentahydroxychalkone separated; after 2 hours 35% had been converted into the orange modification. *iso*Okanin, heated to 180°, quickly re-solidified to an orange product identified through its acetyl derivative (see below) as the *trans*-isomeride.

trans-2 : 3 : 4 : 3′ : 4′-*Penta-acetoxychalkone.*—The natural chalkone (0·5 g.) was heated with anhydrous sodium acetate (1 g.) in acetic anhydride (3 c.c.) for 1 hour at 100°. When the mixture was poured into water, a pale brown oil separated and rapidly solidified, which when crystallised from ethanol gave the *chalkone penta-acetate* (0·67 g., 81%) in colourless needles, m. p. 141°, alone or mixed with synthetic penta-acetoxychalkone (Found : C, 59·4; H, 4·6. $C_{25}H_{22}O_{11},\frac{1}{2}H_2O$ requires C, 59·2; H, 4·55%. Found after drying at 120° : C, 60·1; H, 4·7. $C_{25}H_{22}O_{11}$ requires C, 60·2; H, 4·4%).

cis-2 : 3 : 4 : 3′ : 4′-*Penta-acetoxychalkone.*—*iso*Okanin (0·5 g.) was acetylated as in the case of the *trans*-isomer, and the cis-*penta-acetate* (0·65 g., 83%) obtained as colourless needles, m. p. 113° (Found : C, 60·1; H, 4·5%). Unlike the parent hydroxy-compound it could not be converted into the *trans*-isomer by heating, decomposition occurring to give phenolic products.

trans-2 : 3 : 4 : 3′ : 4′-*Pentahydroxychalkone* 2 : 4-*Dinitrophenylhydrazone.*—(i) A solution of okanin (0·2 g.) in ethanol (1 c.c.) was treated with 2 : 4-dinitrophenylhydrazine (0·15 g.) dissolved in boiling hydrochloric acid (50 c.c.; 2N.). After 5 minutes' boiling, a copious dark red precipitate of the 2 : 4-*dinitrophenylhydrazone* suddenly appeared. This was collected and dissolved in boiling methanol (50 c.c.) from which a crystalline precipitate again appeared after 5 minutes' heating. The product was a scarlet powder (0·25 g.), m. p. 253° (decomp.), which became maroon when heated alone or on attempted crystallisation from high-boiling solvents such as acetic acid or xylene, characteristic very sparingly soluble dark shining platelets being formed (Found : C, 53·7; H, 3·5. $C_{21}H_{14}O_9N_4$ requires C, 53·8; H, 3·4%).

(ii) *iso*Okanin (0·2 g.) was added to a boiling solution of 2 : 4-dinitrophenylhydrazine in hydrochloric acid (50 c.c.; 2N.) whereupon an immediate dark red precipitate was obtained, which in boiling acetic acid or xylene gave glistening plates indistinguishable from those obtained as in (i) (Found : C, 53·6; H, 3·7%).

2 : 3 : 4-*Trihydroxyphenyl* 2-(3 : 4-*Dihydroxyphenyl*)*ethyl Ketone.*—(i) Okanin (21·9 mg.) in ethanol (5 c.c.) was hydrogenated at room temperature and pressure, a palladised charcoal catalyst being used. One mol. of hydrogen (1·85 c.c.) was absorbed during 8 minutes, and a further similar quantity in 90 minutes. Crystalline products could not be isolated either after complete hydrogenation or from the material isolated when reduction was interrupted at the dihydro-stage. However, from the latter a plum-coloured 2 : 4-*dinitrophenylhydrazone* of the dihydrochalkone was obtained as a crystalline powder, m. p. 260° (decomp.) with much previous darkening (Found : C, 51·4; H, 4·6. $C_{21}H_{16}O_9N_4,H_2O$ requires C, 51·6; H, 4·1%).

(ii) When *iso*okanin (27·4 mg.) was reduced as in (i) two mols. of hydrogen (4·4 c.c.) were steadily absorbed, the absorption–time plot being a continuous curve. In the presence of sodium hydroxide (0·1 c.c. of 2N., *ca.* 2 equivs.) reduction was much slower and had nearly ceased after the uptake of one mol. The product was converted into a 2 : 4-dinitrophenylhydrazone identical in appearance, decomposition point, and *X*-ray diffraction pattern with that prepared from the *trans*-isomer (Found : C, 51·1; H, 4·1%).

5-(3 : 4-*Dihydroxyphenyl*)-3-(2 : 3 : 4-*trihydroxyphenyl*)-1-*phenyl*-Δ^2-*pyrazoline* (III).—(i) Okanin (0·15 g.) was heated with phenylhydrazine (0·07 g., 1·25 mols.) in boiling ethanol (5 c.c.) for 2 hours. The addition of water precipitated an oil which was separated by decantation, dissolved in alcohol (1 c.c.), and reprecipitated with water. No crystalline material could be obtained from the resulting product but, after it had been heated at 100° with acetic acid (1 c.c.) for 1 hour, the addition of water gave the solid *pyrazoline* (III) (79 mg., 40%) which crystallised from aqueous ethanol in small, very pale straw-coloured tablets, m. p. 157° (Found, in an air-dried sample : C, 63·3; H, 5·4; N, 7·6. $C_{21}H_{18}O_5N_2,H_2O$ requires C, 63·6; H, 5·05; N, 7·1. Found, after drying at 120° : C, 66·4; H, 4·4; loss, 5·4. $C_{21}H_{18}O_5N_2$ requires C, 66·7; H, 4·7; loss, 4·6%).

(ii) A solution of *iso*okanin (0·2 g.) and phenylhydrazine (0·1 g., 1·3 mols.) in ethanol (2 c.c.) was kept for 24 hours at 0°. The cis-2 : 3 : 4 : 3′ : 4′-*pentahydroxychalkone phenylhydrazone* precipitated by adding water crystallised on scratching and gentle warming. It separated as a hemihydrate from cold aqueous ethanol as minute cream-coloured prisms (91 mg., 35%), darkening on exposure to air and light, m. p. 175° (Found, in air-dried sample : C, 65·3; H, 4·7; N, 6·8. $C_{21}H_{18}O_5N_2,\frac{1}{2}H_2O$ requires C, 65·1; H, 4·9; N, 7·2. Found, after drying at 70° *in vacuo* : C, 66·9; H, 5·0. $C_{21}H_{18}O_5N_2$ requires C, 66·7; H, 4·7%). When heated with acetic acid, or in ethanol at 100° for 30 minutes, the phenylhydrazone was converted into the pyrazoline, m. p. 157°, identical with that prepared from okanin. The pyrazoline was also the sole product when *iso*okanin and phenylhydrazine reacted at 100°.

Determinations of ultra-violet spectra were made with a Unicam spectrophotometer generously provided by Imperial Chemical Industries Limited.

THE UNIVERSITY, NOTTINGHAM. [*Received, November 21st,* 1950.]

123. *The Vapour-phase Oxidation of Methylcyclopentane.*

By J. H. Burgoyne and J. A. Silk.

The pressure–temperature limits for spontaneous cool- and hot-flame ignitions of an equimolecular methyl*cyclo*pentane–oxygen mixture in a 550-c.c. quartz bulb have been determined, and the effect of the fuel : oxygen ratio has been briefly studied. The progressive changes in concentration of products or product groups in high- and low-temperature slow combustion and cool-flame reactions in the same vessel have also been investigated. Similarly, the products formed in a Pyrex-glass flow system at atmospheric pressure have been studied for different fuel : oxygen ratios and for an equimolecular mixture at varying residence times, all the reacting media being diluted with an equal volume of nitrogen. The chief stable products, apart from the oxides of carbon, are carbonyl compounds (including ketones), acids (particularly at low temperature), and unsaturated materials (particularly at high temperature). Peroxides survive in the products at low temperatures. Reaction in a flow system is initiated at an area of the reactor which has become " activated," and the position of this area varies with the flow rate.

The increasing exploitation of petroleum as a raw material for the chemical industry has renewed interest in the homogeneous oxidation of hydrocarbons as a possible means of deriving useful intermediates. Methyl*cyclo*pentane, the subject of the present study, is available from the processing of petroleum.

Only a few chemical investigations into the vapour-phase oxidation of the cyclic paraffins generally, and of methyl*cyclo*pentane in particular, have been reported. Lewin (*Bull. Soc. chim. Belg.*, 1933, **42**, 141) studied a number of alkyl*cyclo*paraffins, including methyl*cyclo*pentane, using reaction temperatures of less than 250°, the induction period for the oxidation of methyl*cyclo*pentane then being several hours. Ivanov (*J. Gen. Chem. Russia*, 1936, **6**, 470; *Chem. Abs.*, 1936, **30**, 6344) has described the properties of the peroxides obtained by the oxidation of *cyclo*hexane with air in a flow system at 316°, and tentatively ascribes the structures $(HO{\cdot}O)_3C_6H_9{\cdot}O{\cdot}O{\cdot}CH_2{\cdot}OH$ and $HO{\cdot}O{\cdot}C_6H_9(OH){\cdot}O{\cdot}O{\cdot}CH_2{\cdot}OH$ to the peroxides. Presumably these products are obtained by interaction of formaldehyde and *cyclo*hexyl peroxide initially formed.

Dupont and Chavanne (*Bull. Soc. chim. Belg.*, 1933, **42**, 537) studied the slow oxidation of ethyl-, butyl-, and phenyl-*cyclo*pentane, below their boiling points. From ethyl*cyclo*pentane were obtained heptan-3-one, 5-ketoheptanoic, propionic, acetic, and formic acids, as well as hydrogen and oxides of carbon. It was concluded that oxidation leads first to rupture at the tertiary carbon atom.

It is well known that in order to obtain useful yields of oxygenated intermediates by the homogeneous oxidation of hydrocarbons it is necessary to work with mixtures containing oxygen in less than stoicheiometric proportions and at temperatures and pressures somewhat below those necessary for ignition. Except for first members of homologous series the relation of pressure with temperature along the ignition limit is rarely simple. The complexities encountered are well illustrated in Newitt and Thorne's investigation (*J.*, 1937, 1656, 1669) into the oxidation of propane. It was therefore clear that, before considering the oxidation products obtainable from methyl*cyclo*pentane, it would be necessary to define the range of conditions to be covered. The ignition limits under static conditions were therefore surveyed and the progressive formation of reaction products was examined under certain typical conditions thus indicated. For the purpose of obtaining products efficiently, however, a continuous reaction system is essential, and with the knowledge obtained from " static " reactions the investigation of products was extended into a flow system.

A complex mixture of oxidation products is to be expected from a molecule of the size of methyl*cyclo*pentane. For preliminary survey, therefore, groups rather than individual compounds were in most cases determined. The work has not proceeded beyond this point, but it sets the stage for a more detailed study of individual products under selected conditions of reaction.

Experimental.

Materials.—Methyl*cyclo*pentane was prepared from *cyclo*hexane by isomerisation in the presence of aluminium chloride, followed by fractionation through a twenty-plate column and removal of aromatic

compounds by silica gel. It was spectroscopically free from benzene but may have contained up to 5% of *cyclo*hexane.

Oxygen (99·5%), from cylinders, was stored over water in a glass gas-holder and before use was passed successively over silica gel and anhydrous magnesium perchlorate.

Apparatus and Method.—Static oxidation. The apparatus used for the "static" experiments has been described by Burgoyne (*Proc. Roy. Soc.*, 1937, *A*, **161**, 48). It consists essentially of a system for preparing a small stock of hydrocarbon–oxygen mixture (with added nitrogen if desired) of which a part can be introduced into an evacuated 550-c.c. cylindrical quartz reaction vessel at a known temperature to give the required pressure. Subsequent reaction is observed with the aid of a mercury manometer. For analysis of the products formed at intermediate stages of the reaction, the apparatus was extended by connecting to the reaction vessel, through a stopcock, a 500-c.c. bulb with a mercury manometer attached, followed by a gas burette. The bulb was evacuated and immersed in carbon dioxide–alcohol.

To withdraw the products from the reaction vessel, the stopcock to the cold evacuated bulb was opened, most of the reacting mixture then flowing quickly into the bulb. The proportion removed from the reaction vessel was ascertained by an immediate reading of the reaction manometer. To obtain a suitable amount of material for analysis the reaction and the process of sampling were repeated 3—10 times, depending on the pressures of reactants which could be admitted to the bulb without causing ignition. The gas pressure in the sampling bulb at the temperature of solid carbon dioxide was then noted and a gas sample pumped out with the aid of a gas burette. The bulb was allowed to warm to room temperature and the remaining products were dissolved and washed out with water. The washings were made up to a standard volume, from which aliquot parts were withdrawn for analysis. The small amount of water-immiscible matter was dispersed by vigorous shaking before withdrawal of portions of the mixture for analysis.

Flow-oxidation apparatus. In principle the method was to pass streams of oxygen and of nitrogen, saturated with methyl*cyclo*pentane at various temperatures, by way of separate pre-heating tubes to a mixing spiral (10-ml. capacity) and 3·2-cm.-diameter cylindrical Pyrex reaction chamber (83-ml. capacity), all enclosed in an electric furnace. Immediately after leaving the furnace the gas stream passed through a water-cooled condenser into a cooled receiver.

The furnace temperature was accurately controlled by an air-bulb thermoregulator operating through a 200-watt auxiliary heater traversing the length of the furnace tube. Under steady conditions this gave control within 2°, but the regulator could only compensate to a limited extent for local temperature rises occurring in the reaction chamber. Temperatures were measured by a roving Pt/Pt–Rh thermocouple which, however, rested for the most part on top of the reaction chamber. The part of the furnace occupied by the mixer and reactor was uniform in temperature within 5°.

With this apparatus residence times of 2—40 seconds were possible, and, in the results that follow, residence time should be understood to mean that which would apply without change in volume caused by exothermic reaction or by change in the number of molecules through reaction; in most of the experiments the divergence from the true residence time did not exceed 10%. At 300° it was possible to run the system at a standard pressure of 760 mm. with the aid of an arrangement of mercury bubblers connected with a water-pump, but at higher temperatures it was necessary to work at the prevailing atmospheric pressure to avoid ignitions resulting from sharp changes in the working pressure.

On account of mist formation a receiver cooled in solid carbon dioxide was not satisfactory, and a sintered-plate bubbler containing solvent and cooled in ice was more suitable; gas samples were withdrawn after they had passed the bubbler.

In general, *iso*propanol was the best solvent for absorption of the products, including water, together with excess of hydrocarbon, but owing to interference of *iso*propanol with some of the analytical methods the products were collected in water; the aqueous and the hydrocarbon layer were separated and each made up to a definite volume (the latter with pure *cyclo*hexane). Equal proportions of each solution were then taken for each determination, excepting that of formaldehyde which was found exclusively in the aqueous part; higher aldehydes could not satisfactorily be determined owing to their presence in part in the hydrocarbon layer.

Methods of Analysis.—Gases. The gas sample was analysed in a Bone–Newitt constant-volume apparatus, using potassium hydroxide solution for carbon dioxide, alkaline pyrogallol for oxygen, mercuric perchlorate for olefins (R. A. Cox, personal communication), and ammoniacal cuprous chloride for carbon monoxide. The residue was exploded with a measured volume (A) of oxygen in excess, and the carbon dioxide (B) formed was measured. Residual oxygen (C) was then absorbed, and also the small but erratic volume of carbon monoxide (D) evolved from the pyrogallol. (B) gave the quantity of paraffinic carbon; and from the oxygen consumed, $[A - (C + D)]$, the total of paraffinic and free hydrogen was calculated, after allowance for oxygen required to form carbon dioxide.

Liquids. After considerable investigation, the following methods were adopted.

(1) Acids. Titration with N/50-alkali, to phenolphthalein or α-naphtholphthalein.

(2) Peroxides. Two iodometric methods were used together: (*a*) A 5-ml. sample was added to acetic acid (15 ml.) containing 50% aqueous potassium iodide (2 ml.) (iodine liberated by peracetic acid being removed previously with sodium thiosulphate). After at least 1½ hours, the solution was diluted with water and titrated with N/50-thiosulphate. (*b*) (Based on Clover and Houghton's method, *Amer. Chem. J.*, 1904, **32**, 43.) The sample was added to 50% potassium iodide solution (2 ml.), and the following procedures carried out: (i) the mixture was kept for 10 minutes and then titrated with sodium thiosulphate; (ii) the mixture was treated with 20% sulphuric acid, kept for a further 30 minutes and titrated again; (iii) iodine liberated after this mixture had been kept overnight was titrated; and (iv)

iodine liberated after the addition of a trace of ferrous salt was titrated. In practice no significant readings were obtained in steps (iii) and (iv), from which it was concluded that alkyl hydroperoxides and dialkyl peroxides were not present in appreciable quantity. In methods (*a*) and (*b*) closed flasks were used from which air was displaced by nitrogen.

(3) *Total carbonyl compounds.* A hydroxylamine reagent was prepared by dissolving hydroxylamine hydrochloride (10 g.) in water (100 ml.), dilution to 1 l. with alcohol, and adjustment of the pH to the dichroic neutral point of bromophenol-blue by addition of alkali. 70 ml. of the reagent with 10 ml. of sample were warmed at 50° for 30 minutes; after cooling, the mixture was treated with 1 ml. of 0·2% bromophenol-blue, and the solution titrated with N/30-alkali to the colour of a blank containing the same volume of water.

Such evidence as is available indicated that under the conditions of this determination, hydroxyperoxides, which may be formed from aldehydes and hydroperoxides in the products, dissociate into the original components. Small quantities of hydrogen peroxide were found not to interfere, and there appeared to be little reaction of organic peroxides during the period of the determination, since subsequent heating of samples containing peroxides resulted in a *slow* liberation of hydrochloric acid which required several hours for completion. No correlation was found, however, between the acid thus liberated and the quantity of peroxides determined iodometrically.

(4) *Formaldehyde.* The colorimetric test described by Steigmann (*J. Soc. Chem. Ind.*, 1942, **51**, 18) was adapted for quantitative use. The reagent consisted of an aqueous solution of magenta (Technical) (0·025% w/v), sulphuric acid (2·5% v/v), and thiolacetic acid (0·03—0·05% w/v). The acid dye solution was kept for several hours before addition of the thiolacetic acid, and the reagent was freshly prepared every few days. After an approximate determination by comparison with a series of standards in which the formaldehyde contents were in geometric progression with a ratio of 1·6, the colour developed by the appropriate volume of sample was compared after 10 minutes with that of a series of standards prepared from 5 ml. of reagent and severally 1·0, 1·1, 1·2, 1·3, 1·4, 1·5, 1·6 ml. of 0·0075M-formaldehyde. Under these conditions interference effects were least pronounced.

(5) *Higher aldehydes.* The colorimetric method using Schiff's reagent was employed, with aqueous propaldehyde as standard.

(6) *Ketones.* These were deduced by difference, *i.e.*, total carbonyl — (formaldehyde + higher aldehydes).

(7) *Unsaturation.* An excess of M/30-bromine in aqueous potassium bromide was run into the sample in about 100-ml. of water, shaken for 30 seconds, and treated with potassium iodide solution. The liberated iodine was titrated with thiosulphate. By working in dilute neutral solution and titrating the iodine promptly, peroxide interference was largely avoided, and the reaction of higher aldehydes minimised.

(8) *Alcohols.* The acetyl chloride–pyridine method of Smith and Bryant (*J. Amer. Chem. Soc.*, 1935, **57**, 61) was employed. For this analysis separate reactions were carried out and the products collected in toluene instead of water. The receivers were washed out with dioxan to remove water, and the final solution was dried with anhydrous sodium sulphate before analysis. The method was satisfactory only in the absence of peroxides.

Results and Discussion.

Zones of Reaction.—The observed modes of reaction of an equimolecular methyl*cyclo*pentane–oxygen mixture in relation to temperature and pressure are set out in Fig. 1. The general form of the diagram is typical of the higher paraffins and it differs only in detail. Figures attached to points on the boundary curves represent measured delays between admission of the mixture to the reaction vessel and the occurrence of cool-flame or true ignition as the case may be.

Ignition near the limit at high temperatures was always followed by some slow combustion which increased in extent with increasing temperature. Over most of the cool-flame region three successive pulses were observed in each reaction; and in the ignition zone within the cool-flame temperature range (245—365°) two cool-flame pulses preceded each ignition.

The state of the surface of the reaction vessel exerted a strong influence on the results obtained both for delay periods and for the actual limits of cool-flame or true ignition. To standardise conditions, it was best to prepare the vessel by carrying out a few mild ignitions at high temperatures. Between tests the vessel was first evacuated roughly, then swept out with air for half a minute, and finally evacuated fully.

A few cool- and hot-flame ignition-limit determinations were made with 1 : 2 and 2 : 1 methyl*cyclo*pentane–oxygen and 1 : 1 : 4 methyl*cyclo*pentane–oxygen–nitrogen mixtures. The results are compared with data for the equimolecular mixture, taken from Fig. 1, in Table I, the nitrogen mixture being calculated to a nitrogen-free basis. It will be seen that the cool-flame limit is not greatly affected by composition but is lowered in the presence of nitrogen. The hot-flame limit rises throughout the temperature range on increasing the proportion of hydrocarbon, but is lowered in the presence of nitrogen. With the 2 : 1 mixture not more than two successive cool flames were observed in any one reaction, but with the 1 : 2 mixture as many as five successive cool flames occurred.

TABLE I.

Cool- and hot-flame ignition limits (mm.) for C_6H_{12}–O_2 mixtures.

(H.F. = hot flame; C.F. = cold flame.)

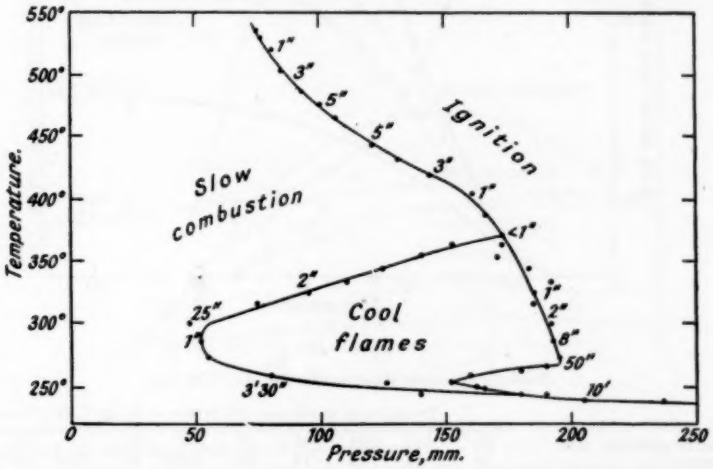
	Ratio C_6H_{12} : O_2.							
	1 : 2.		1 : 1.		2 : 1.		1 : 1(+4N_2).*	
Temp.	H.F.	C.F.	H.F.	C.F.	H.F.	C.F.	H.F.	C.F.
509°	53	—	75	—	†	—	52	—
450	87	—	105	—	†	—	74	—
420	†	—	130	—	156	—	†	—
380	148	—	165	—	205	—	138	125 (?)
340	†	128	183	124	†	138	†	97
315	175	†	195	75	†	73	147	61
274	167	54	195	55	212	62	150	48
255	102	96	152	126	165	124	129	89

* Calc. as partial pressure of the C_6H_{12} : O_2 mixture.
† Not determinable owing to shortness of lags.

Products of Reaction in a Static System.—Consideration of Fig. 1 suggests that there are three zones of reaction requiring study, namely, the cool-flame region and the regions of slow combustion at lower and higher temperatures. Accordingly, conditions of reaction were selected to typify these three zones, and for each condition the progressive formation of products

FIG. 1.

*Combustion diagram for equimolecular methylcyclopentane–oxygen mixture in quartz bulb.**



throughout the reaction was followed. The results are presented in Tables II—IV and in Figs. 2—7.

Yields of products are expressed directly in terms of the number of moles of each obtained from 100 moles of starting material (either methyl*cyclo*pentane or oxygen, the mixture being equimolecular). Since it was impracticable to determine the amount of unchanged hydrocarbon, and the precise nature of the individual products was unknown, carbon balances could not be calculated. An oxygen balance can, however, be obtained if the following overall reactions are assumed irrespective of the actual mechanism :

* *Added in Proof.*—In the light of a recent paper by Malherbe and Walsh (*Trans. Faraday Soc.*, 1950, **46**, 835) we are inclined to believe that the deviations of the experimental points from the smooth limit curves at temperatures below 400° are to some extent significant. Thus pressure minima in the ignition limit are indicated at about 350° and 310° as well as the one shown at about 255°; and the cool flame limit appears to show corresponding features.

$$CH_3 + 1\tfrac{1}{2}O_2 = CO_2H + H_2O$$
$$CH_2 + O_2 = CO + H_2O$$
$$CH + O_2 = CO_2H$$
$$CH + \tfrac{1}{2}O_2 = C{\cdot}OH$$
$$CH{\cdot}CH + \tfrac{1}{2}O_2 = C{:}C + H_2O$$
$$R{\cdot}CO_2H = RH + CO_2$$
$$R{\cdot}CHO = RH + CO$$

These equations do not, however, take into account the fission of C–C bonds, which would be equivalent to oxidation.

High-temperature Reaction (450° and 100 mm.) (see Table II and Figs. 2 and 3).—Observable

FIG. 2.

Gaseous products from equimolecular methylcyclopentane–oxygen mixture at 450° *and* 100 *mm.*

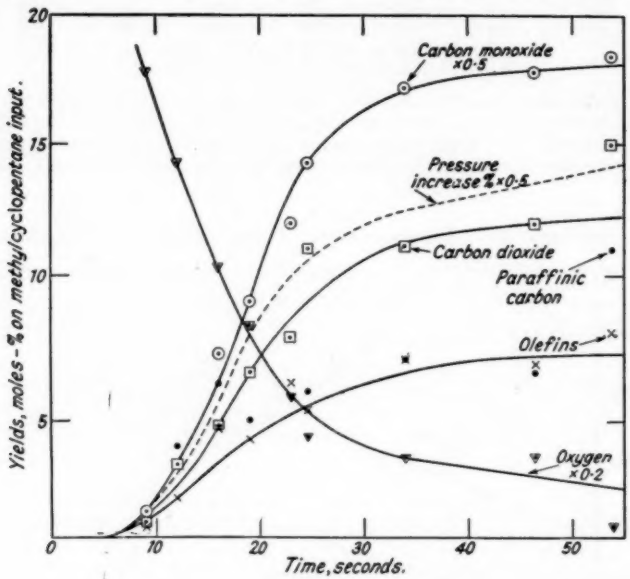


TABLE II.

High-temperature reaction at 465° *and* 100 *mm.*

	Products in moles per 100 moles of O_2 (or C_6H_{12}) input.									
Mean initial pressure, mm.	93	101	101	96	97	104	96	97	104	109
Time, secs.	9	12	16	19	23	24·5	34	46·5	54	75
Pressure increase (% of initial)	2	5	10	15	20	21·5	25	27·2	28·4	30
Carboxyl	0·25	0·3	0·5	0·7	0·75	0·75	0·85	1·05	0·65	0·6
Carbonyl total	2·6	5·4	11·0	13·4	16·0	16·25	17·85	16·9	17·0	14·9
Formaldehyde	1·4	1·8	2·7	3·8	4·1	4·2	5·2	5·45	5·8	—
Higher aldehyde	1·5	2·5	4·9	6·0	7·3	6·7	8·9	7·7	5·55	—
Ketone	(−0·5)	1·2	3·4	3·4	4·6	5·4	3·8	3·8	5·6	—
Unsaturation	1·0	2·9	4·2	4·85	5·55	6·4	6·05	5·6	5·55	5·15
Hydroxyl	—	1·2	2·9	2·1	—	—	2·2	—	—	1·9
CO	1·85	5·55	14·05	18·0	24·0	28·3	34·3	35·6	36·75	37·6
CO_2	0·055	2·8	4·3	6·3	7·6	10·9	11·05	12·05	15·1	14·3
Olefins	0·55	1·5	4·2	3·7	5·85	4·85	6·8	6·55	7·35	7·6
Paraffinic C	—	3·5	5·9	4·5	5·35	5·6	6·8	6·3	10·9	13·0
Paraff. and free H	—	6·95	21·4	21·3	25·0	25·1	32·3	32·8	40·5	51·2
Paraff. C/H ratio (from graph)	—	2·0	3·35	4·0	4·0	5·1	4·5	4·65	4·65	4·0
O_2, unconsumed	88·8	72·0	51·6	40·6	27·0	19·7	15·5	15·4	2·15	3·94
O_2, accounted for	95·7	90·5	89·05	87·9	86·2	85·8	93·1	86·3	87·0	86·2

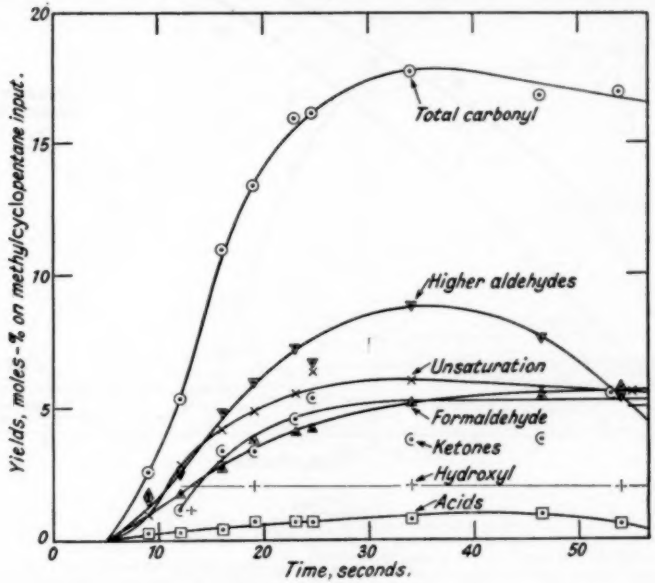
reaction commenced after about 5 seconds, and in the following 20 seconds 50% of the available oxygen was consumed in a relatively fast reaction. Completion of the reaction required a further 50 seconds.

The principal condensable products are carbonyl compounds which reach a maximum concentration, equivalent to 15% of the hydrocarbon input, towards the end of the rapid part of the reaction. The maximum appears to be due to higher aldehydes, for the formaldehyde and ketones, which accumulate during the rapid reaction, remain unchanged or increase slightly throughout the later stages.

The correlation between higher aldehyde concentration and overall reaction rate is consistent with the view that the higher aldehydes are intermediate products in consecutive reactions, though at this temperature there was probably also some pyrolysis. The trends in the ketones, hydroxyl compounds, unsaturated compounds, and (less definitely) acids suggest that they,

FIG. 3.

Condensed products from equimolecular methylcyclopentane–oxygen mixture at 450° *and* 100 *mm.*



like the more obvious end-products carbon monoxide and dioxide and gaseous olefins, are not intermediates but rather end-products of side reactions.

The oxygen balance (Table II) shows that the products analysed account for 85—90% of the oxygen originally introduced. The discrepancy tends to increase slightly throughout the reaction, however, suggesting that there is some product not taken into account. It will be noted that peroxides were not found in the products of this reaction.

Low-temperature Reaction (232° and 400 mm.) (see Table III and Figs. 4 and 5).—At temperatures below the cool-flame range the slow reaction was preceded by a lengthy induction period that was sensitive to temperature and to the condition of the surface of the reaction vessel. For the reaction in question it varied between 10 and 15 minutes, and there were also some variations in the reaction rate. The results given were related to pressure change and thence to time through a standard pressure–time curve typical of the reaction.

An important feature of the results is that half the oxygen is consumed without much pressure increase and practically all is consumed before the pressure increase is more than half complete. In such circumstances the pressure change cannot be taken as a measure of the extent of the reaction (*e.g.*, for kinetic measurements).

The latter part of the reaction must be largely decomposition rather than oxidation, and in the earlier part (induction period) oxygen is apparently reacting without increasing the number of molecules.

When the pressure begins to rise, carbonyl compounds and acids are already present in considerable amount, together with smaller quantities of other products. Comparison with the

FIG. 4.

Gaseous products from equimolecular methylcyclopentane–oxygen mixture at 230° and 400 mm.

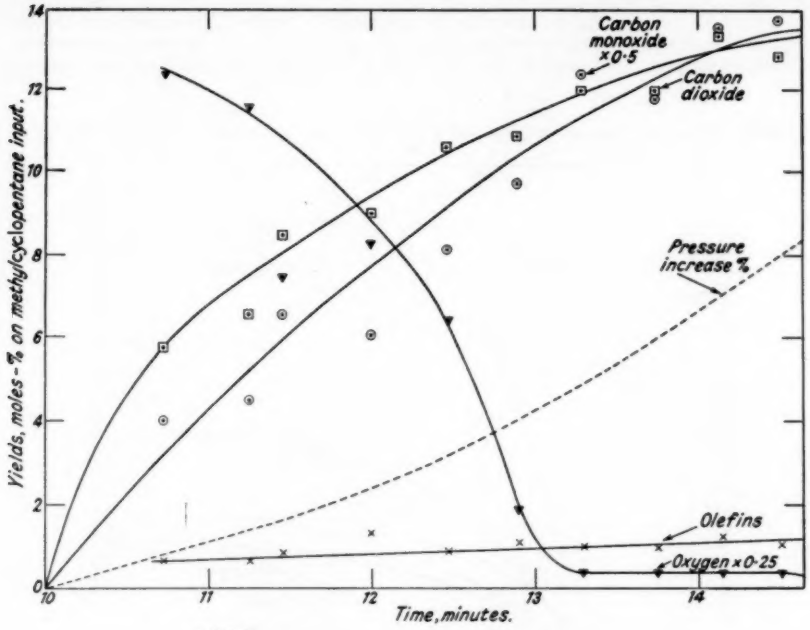


TABLE III.

Low-temperature reaction at 232° and 400 mm.

	Yields in moles of product per 100 moles of O_2 input.									
Pressure increase (% of initial) ...	¾	1¼	1½	2¼	3	4	5	6	7	8
Time, min.	10·8	11·25	11·45	12·0	12·4	12·9	13·3	13·75	14·15	14·5
Mean initial pressure, mm.	398	400	392	401	367	386	397	398	399	402
Carboxyl	5·13	5·8	7·55	7·9	9·9	10·65	11·45	10·45	11·2	11·0
Carbonyl	12·2	13·8	18·93	18·7	22·85	22·9	25·67	23·77	24·9	26·05
Formaldehyde	2·1	2·5	3·0	3·2	4·0	4·6	5·2	4·6	5·3	5·8
Higher aldehydes	4·0	6·3	7·5	6·8	8·7	8·7	8·7	8·2	10·1	8·8
Ketones	6·1	5·0	8·5	8·7	10·1	9·6	11·8	10·9	9·5	12·4
Unsaturation	2·4	1·55	1·85	2·35	2·15	2·15	4·0	2·15	2·85	2·7
Peroxide (*a*)	1·05	1·25	1·3	1·05	1·5	1·65	1·5	1·15	1·15	0·95
(*b*) (i)	0·35	0·45	0·45	0·25	0·3	0·5	0·45	0·2	0·2	0·15
(ii)	0·75	0·75	0·9	0·85	1·15	1·15	1·15	1·0	1·0	0·8
(iii)	0·1	0·1	0·15	0·15	0·2	0·15	0·1	0·15	0·1	0·1
CO	8·25	9·35	13·25	16·95	19·55	24·9	23·7	27·15	27·35	27·35
CO_2	5·85	6·6	8·6	9·05	10·65	10·9	12·05	12·05	13·6	12·8
Olefins	0·7	0·7	0·85	1·35	0·9	1·1	1·0	1·0	1·3	1·1
Paraffinic C	1·9	1·3	1·8	1·3	1·05	0·9	1·85	1·5	2·6	1·75
Paraff. and free H	4·5	3·6	5·1	3·2	3·5	2·5	6·6	4·4	9·0	9·4
O_2, unconsumed	49·85	46·5	30·1	32·95	26·95	7·7	1·55	1·5	1·6	1·45
O_2, accounted for	89·4	90·7	89·1	92·0	100·7	85·7	91·4	85·5	94·2	93·5

results of high-temperature reactions shows ketones and especially acids to be relatively more prominent, whilst unsaturated compounds are in much lower concentration. Peroxides appear in the products in concentration related to the rate of oxygen consumption, and appear to consist chiefly of alkyl hydroperoxides and hydrogen peroxide.

FIG. 5.

Condensed products from equimolecular methylcyclopentane–oxygen mixture at 230° and 400 mm.

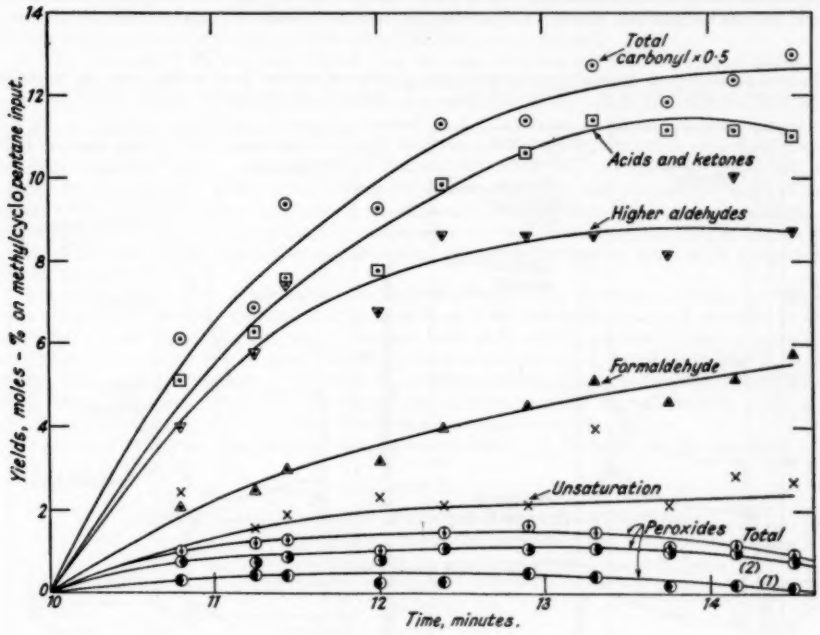


TABLE IV.

Cool-flame reaction at 275° and 155 mm.

	Yields in moles of product per 100 moles of O_2 input.					
Pressure increase (% of initial)	4·7	13·6	15·8	20·5	22·1	26·8 *
Time, min.	2·03	2·1	2·4	2·5	3·5	0·55
Mean initial pressure, mm.	153	156	158	156	156	172
Carboxyl	1·3	2·0	2·7	3·4	3·9	2·3
Carbonyl	6·6	18·2	23·7	27·8	27·2	26·6
Formaldehyde	1·4	4·6	5·2	7·3	8·7	8·5
Higher aldehydes + Ketones	5·2	7·0	6·0	8·0	9·5	11·0
		6·5	12·5	12·5	9·0	7·0
Unsaturation	2·3	3·7	3·6	4·0	4·2	4·9
Peroxide (*a*)	1·1	3·2	3·9	3·2	1·1	0·9
(*b*) (i)	0·5	0·6	1·2	1·5	0·3	0·2
(ii)	0·3	0·4	0·7	0·7	0·6	0·9
(iii)	—	—	—	—	—	—
CO	5·1	17·9	21·9	32·9	38·1	39·6
CO_2	2·1	4·9	5·8	7·6	10·9	11·9
Olefins	0·7	2·2	2·8	3·6	3·5	3·6
Paraffinic C	—	3·2	1·9	3·5	4·1	2·5
Paraff. and free H	—	9·6	8·1	11·2	14·1	10·3
O_2 unconsumed	83·7	42·0	31·9	8·5	1·8	2·1
O_2, accounted for	103·0	94·6	97·4	97·5	94·3	94·7

* Products at end of reaction at 300°.

The continued pressure increase in the later stages of reaction is clearly associated with the formation of oxides of carbon, but apart from a limited disappearance of peroxides and perhaps acids and ketones there is no definite indication of the source of carbon monoxide and dioxide at this stage. The higher aldehydes survive a great deal better than at high temperatures.

Generally speaking (see Table III) 90% or more of the oxygen introduced is accounted for in the products analysed, and the balance tends to improve in the later stages of the reaction.

Cool-flame Reaction (275° and 155 mm.) (see Table IV and Figs. 6 and 7).—Under these conditions an induction period of about 110 seconds is followed by 15 seconds of slow combustion with very little pressure change, terminating in two cool flames in quick succession; after a

FIG. 6.

Gaseous products from equimolecular methylcyclopentane–oxygen mixture at 275° and 160 mm.

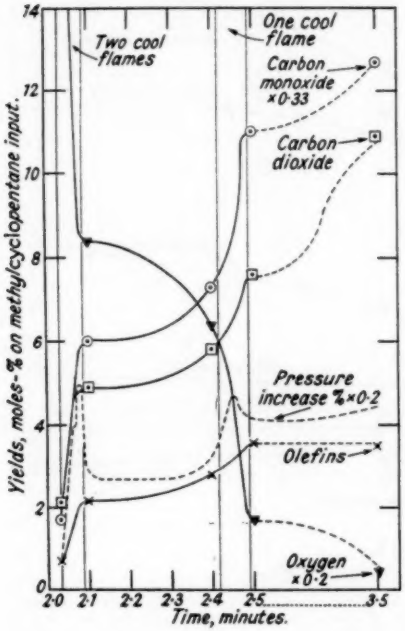
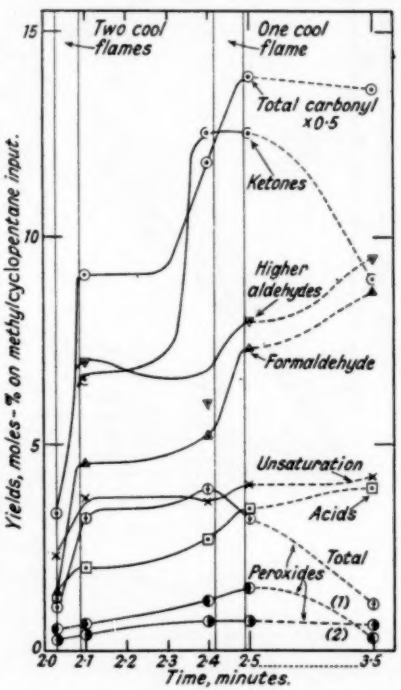


FIG. 7.

Condensed products from equimolecular methylcyclopentane–oxygen mixture at 275° and 160 mm.



further 20 seconds a feebler cool flame is propagated and this is followed by a final stage of slow combustion. It was not possible to interrupt the reaction between the first and second cool flames.

In all, two-thirds of the oxygen is consumed during the three cool flames, and the product concentrations, excepting that of peroxides, show corresponding step-wise increases. In general terms, the distribution of products resembles that in the low-temperature slow reaction more than that in the high-temperature reaction, but acids are less prominent and unsaturated compounds more so, in accordance with the intermediate temperature. The total peroxide content determined by method (*a*) is usually much greater than that determined by method (*b*).

The results for aldehydes are in agreement with the findings of Neumann and Aivazov (*Acta Physicochim. U.S.S.R.*, 1936, **4**, 575) for pentane, but not with those of Newitt and Thorne (*loc. cit.*) for propane, in showing that aldehydes increase during the passage of cool flame.

More than 94% of the oxygen introduced was accounted for throughout this reaction (see Table IV).

Oxidation in a Flow System.—Mixtures were found to be much less prone to ignition in the flow system than in the static apparatus, and it was possible, therefore, to work at considerably higher partial pressure of reactants. Mixtures containing 50% of nitrogen were generally the most convenient: with them the temperature rise at the walls of the reactor was rarely more than 20°. Investigation of the effect of residence time as a measure of the extent of oxidation was difficult, owing both to surface effects (see below) and to the rapidity of reaction over most of the temperature range (250—500°) which could be studied. As an alternative the effect of varying the proportion of oxygen in the initial mixture was examined.

Surface influences. It was soon found that, in order to establish reaction in the region of 300°, the mixture had first to be passed through for a few minutes at a long residence time, *e.g.*, about 30 seconds. Reaction thus established persisted as the residence time was reduced slowly: a sudden reduction, however, caused it to die away. About 10 minutes after establishment of the reaction at the working temperature, product formation was steady and sampling could be begun. Interruption of the reaction even for 1—2 minutes led to loss of activity of the reactor. These observations emphasise the important role of the state of the reactor surface in determining the rate of reaction, and indicate that for given flow conditions the reaction is initiated in a certain region of the reactor where the surface has become activated. A change in flow rate evidently necessitates that the activated region must shift to another part of the reactor surface.

Cool-flame and ignition phenomena also showed the influence of surface conditions. Thus, when the nitrogen content was maintained at 50% and the residence time at 7 seconds, it was found that at 300° increasing the oxygen content from 25% to 30% resulted in the propagation every 9 seconds of a pair of cool flames, of which the first was the more vigorous; further increase to 35% gave periodic, inaudible, yellow-flame ignitions, and subsequent decrease to 30% then gave a feeble cool flame followed by a yellow-flame ignition; further decrease to 25% of oxygen gave neither cool flames nor ignitions. This cycle of events was reproducible.

Products of oxidation; variation of mixture composition. In Table V are the results of two

TABLE V.

Effect of C_6H_{12} : O_2 *ratio on products at* 300° (*7-secs. residence*).

(*a* and *b* are duplicate runs).

Yields in moles of product per 100 moles of O_2 input.

	1		1·5		2		3		5	
C_6H_{12} : O_2	*a.*	*b.*	*a.*	*b.*	*a.*	*b.*	*a.*	*b.*	*a.*	*b.*
Carboxyl	3·7	3·6	3·8	3·3	3·35	2·95	2·8	2·85	3·45	3·7
Carbonyl, total	22·8	25·6	25·7	26·0	26·1	27·4	29·1	26·8	38·9	33·4
Formaldehyde	3·9	3·9	4·8	4·25	4·85	4·8	5·55	5·6	7·05	7·05
Unsaturation	11·8	10·5	12·7	12·3	13·7	13·3	13·95	13·35	18·7	17·55
Peroxides (*a*)	4·6	6·05	5·75	4·85	3·65	4·4	3·1	2·3	3·65	3·35
(*b*) (i)	1·9	2·3	1·9	2·05	1·75	1·75	1·35	1·55	1·55	2·15
(ii)	1·0	0·7	1·15	1·45	1·45	1·3	1·75	2·1	3·2	2·95
(i + ii)	2·9	3·0	3·05	3·5	3·2	3·05	3·1	3·65	4·75	5·1
CO	37·6	39·2	29·5	29·6	26·8	26·8	26·4	26·4	28·7	27·6
CO_2	6·5	6·75	4·75	5·15	4·4	5·1	3·75	2·85	3·6	4·4
Olefins	6·7	5·2	3·9	5·05	3·8	5·75	3·6	3·2	4·05	3·2
O_2, unconsumed	9·8	10·4	17·3	17·85	20·5	21·55	22·4	21·9	18·7	16·0
O balance	99·3	104·7	99·4	99·6	97·4	101·7	99·6	94·8	111·9	100·7
RR'CO : CH_2O	6·2		5·8		5·55		5·0		(5·5)	4·75
RR'CO + CO	60·4	64·8	55·2	55·6	52·9	54·2	55·5	53·2	67·6	61·0

identical series of runs (*a* and *b*) made at 300° with 7-seconds residence time and methylcyclopentane–oxygen ratios from 1 to 5, all the mixtures being diluted with an equal volume of nitrogen; the runs in each series were carried out in the order of decreasing oxygen content.

When regard is paid to the factors already discussed, the concordance of the results is good. It is evident that the survival of carbonyl and condensable unsaturated compounds is favoured by a low proportion of oxygen, the proportion of gaseous products being at the same time reduced. In general the results are like those obtained at intermediate stages in the oxidation of the equimolecular mixture under static conditions (Table III), except that the yield of condensable unsaturated compounds is several times greater in the flow experiments. A low proportion of oxygen in the mixture is associated with a high yield of formaldehyde compared

with other carbonyl compounds, but the combined yields of carbonyl compounds plus carbon monoxide remain approximately constant throughout the series.

The variation in formaldehyde yield with hydrocarbon concentration finds an explanation in Walsh's hypothesis (*Trans. Faraday Soc.*, 1947, **43**, 297) that primary peroxide radicals, which in this case would be formed after fission of the *cyclo*pentane ring, are relatively unstable and decompose to give a higher aldehyde. With increase in hydrocarbon concentration a greater proportion would react to form primary peroxide molecules, and these on decomposition would yield formaldehyde :

$$R{\cdot}CHO + OH \longleftarrow R{\cdot}CH_2{\cdot}O{\cdot}O \xrightarrow{R'H} R{\cdot}CH_2{\cdot}O{\cdot}OH \longrightarrow R + CH_2O + OH$$

A comparison of the results for peroxides demonstrated the limitations of the analytical methods employed : method (*a*) shows a maximum when the methyl*cyclo*pentane–oxygen ratio is lowest, but method (*b*) shows an opposite result. Peracids vary little throughout and the discrepancy appears to be associated with the peroxides which react only in acid solution. Oxygen balances are very satisfactory.

The results for a similar series of runs at 465° with a 4·5-seconds residence time are given in Table VI. Here the chief differences from the static reaction (cf. Table II) are again in the

TABLE VI.

Effect of C_6H_{12} : O *ratio on products at* 465° (4·5-*secs. residence*).

	Yields in moles of product per 100 moles of O_2 input.					
C_6H_{12} : O.	1 •	1	1·5	2	3	5
Carboxyl	0·95	0·9	1·2	1·0	1·0	1·05
Carbonyl, total	16·75	15·25	19·65	19·9	18·4	25·9
Formaldehyde	5·25	5·1	6·0	7·4	5·3	9·25
Unsaturation	29·0	20·2	38·7	46·5	53·8	69·5
Peroxides (*a*)	0	0·1	0·1	0·15	0·15	0·4
CO	56·7	58·1	41·9	39·65	31·0	34·0
CO_2	7·2	5·75	5·75	4·80	7·1	5·8
Olefins	47·5	48·6	42·7	38·5	29·55	25·8
O_2, unconsumed	3·7	5·35	2·6	2·1	1·1	0·7
O_2, accounted for	127·7	122·2	115·4	113·0	104·5	117·9
O_2, accounted for excluding olefins	103·9	98·9	94·0	93·8	89·7	105·0

• Results from another series of experiments.

higher yields of unsaturated compounds, both liquid and gaseous, obtained in the flow reaction. Yields of peroxides are negligible. The high oxygen balances are probably accounted for by cracking, which is known to be induced by oxygen at moderately high temperatures. If, as an approximation, the gaseous olefins are considered to be formed without oxygen consumption, reasonable balances are restored.

Observations upon the effect of varying the partial pressure of nitrogen associated with an equimolecular methyl*cyclo*pentane–oxygen mixture at 300° showed that a fairly distinct limit is encountered between 71·5% and 73·5% of nitrogen at which reaction becomes much reduced. At 350° this limit lies beyond 78% of nitrogen.

TABLE VII.

Effect of residence time on products from 1 : 1 : 2 C_6H_{12}–O_2–N_2 *at* 300°.

	Yields in moles of product per 100 moles of O_2 input.				
Contact time, secs.	2·5	3·33	4·5	6	8
Carboxyl	1·65	2·1	3·0	3·35	2·6
Carbonyl	15·4	15·9	19·7	22·3	22·4
Formaldehyde	3·4	3·4	3·8	5·2	4·4
Unsaturation	10·0	9·7	10·3	13·7	12·0
Peroxide (*a*)	3·5	4·0	4·3	4·2	2·7
(*b*) (i)	1·0	1·1	1·5	1·7	1·4
(ii)	0·4	0·4	0·6	0·8	0·6
CO	18·9	20·8	30·3	30·8	33·1
CO_2	4·0	3·7	5·9	6·0	6·7
Olefins	5·1	3·6	5·4	5·3	6·2
O_2, unconsumed	42·8	37·0	31·9	21·0	10·6
O_2, accounted for	96·6	93·1	107·4	101·8	91·8

Variation of residence time. With the 1 : 1 methyl*cyclo*pentane–oxygen mixture diluted with nitrogen at 300° it was possible to some extent to find flow rates giving intermediate oxygen consumptions, in spite of a greater temperature rise caused by reaction with increasing flow rates. Analyses of products of the 1 : 1 : 2 methyl*cyclo*pentane–oxygen–nitrogen mixture over a range of residence times were therefore made, with the results shown in Table VII. At the two shortest residence times feeble cool flames were propagated through the reactor in pairs at intervals of about 3 seconds. Except for the carbonyl compounds, all the liquid products reach maximum yields at 6-seconds residence time, but the oxygen balances are rather erratic and it is difficult to draw detailed conclusions.

In Table VIII are given further results relating to the same 1 : 1 : 2 mixture reacting for

TABLE VIII.

Effect of temperature and residence time in products from 1 : 1 : 2 *and* 1 : 1 : 4 C_6H_{12}–O_2–N_2 *mixtures.*

	Yields in moles of product per 100 moles of O_2 input.											
$C_6H_{12} : O_2 : N_2$ ...	1 : 1 : 2		1 : 1 : 2		1 : 1 : 2		1 : 1 : 2			1 : 1 : 4		
Temp.	300°		350° *		400° *		465°			510°		
Residence time, secs.	4·5	8	4·5	8	4·5	8	2·5	4·5	8	2·5	4·5	8
Carboxyl	3·0	2·6	Not determined				1·0	1·0	1·3	0·9	1·0	0·9
Carbonyl	19·7	22·4	22·2	22·5	19·6	19·3	15·7	16·8	21·1	14·4	16·6	18·1
Formaldehyde	3·8	4·4	Not determined				6·0	5·3	6·8	5·4	5·5	5·8
Unsaturation	10·3	12·0	24·1	14·5	24·7	19·2	23·8	29·0	31·3	14·7	17·7	18·5
Peroxide (*a*)	4·3	2·7	1·7	1·0	trace	0	0	0	0	0	0	0
CO	30·3	33·1	44·1	41·0	54·3	32·3	50·8	56·7	43·7	62·6	60·4	48·7
CO_2	5·9	6·7	6·9	9·5	8·0	11·3	7·8	7·2	7·7	6·3	7·6	7·4
Olefins	5·4	6·2	18·5	9·4	31·0	8·7	56·4	47·5	29·6	70·0	57·8	42·7
O_2, unconsumed ...	31·9	10·6	2·9	3·2	4·3	2·9	6·2	3·7	2·3	6·2	5·9	3·1
O_2, accounted for ...	107·4	91·8	102·5	93·3	119·1	85·4	125·0	127·8	111·0	136·9	133·6	113·0
O_2, accounted for excl. olefins	104·7	88·7	93·2	88·6	102·6	81·1	97·8	104·0	96·2	101·4	104·7	91·7
Temp. rise	24°	20°	29°	11°	23°	5°	20°	9°	3°	8·5°	3°	1°

* The balances for products formed at 350° and 400° are exclusive of carboxyl.

certain times at 350°, 400°, and 465°. At 510° this mixture ignited and the 1 : 1 : 4 mixture was used instead. Relevant results for 300° are quoted from Table VII for comparison. At 350° and 400° the heat of reaction was too great to allow the 2·5-seconds residence time to be investigated. At 350° no preliminary activation of the reactor was necessary, although it took five minutes for the temperature rise to reach its stationary value.

In general, increase in temperature favours the gaseous at the expense of liquid products. Gaseous olefins show a pronounced increase, and the oxygen balances indicate that they arise mainly by pyrolysis. Their decrease with increasing residence time is attributable to polymerisation, which is known to be induced by small quantities of oxygen.

The reduction in exothermicity as the reaction temperature is raised is not adequately accounted for by the smaller input of reactants needed to maintain a given residence time, but it is paralleled by the increases in unsaturated products; the oxygen balances show that these must be formed mainly by cracking, and this is known to be an endothermic process.

Up to at least 465° the yield of formaldehyde increases with temperature. The decrease in carbon monoxide production with increase in residence time from 4·5 to 8 seconds is rather surprising. Oxygen consumption at this stage is practically complete, and, since carbon dioxide does not show a corresponding increase, neither direct oxidation nor the water gas equilibrium can be invoked as an explanation. It is perhaps significant that the increase in production of carbonyl compounds when residence time is increased from 2·5 to 8 seconds at 465° and 510° is slightly greater than the oxygen consumption during this period. Moreover, in all the series of experiments from 300° to 500° the oxygen balance (excluding olefins) is highest (or higher) when the contact time is 4·5 seconds, so that it is unlikely that these observations are attributable to experimental error.

Oxidation below 300°. For the purpose of investigating reactions below 300° the 2 : 2 : 1 mixture of methyl*cyclo*pentane, oxygen, and nitrogen was employed with a 40-seconds residence time. The reaction was self-initiating down to about 280°, but, on further lowering of the temperature, reaction died away at about 255°, signalled by a pair of cool flames or feeble ignitions. On slow raising of the temperature again, inaudible, blue-flame ignitions with a

period equal to the residence time set in at 265°, and shortly gave way to cool flames every 15 seconds.

Since this is in the region of the low-temperature ignition peninsula (see Fig. 1), the transition from ignition to cool flames could be accounted for by a slight temperature rise. Continuous cool-flame propagation was never observed when starting from a high temperature.

At 260—265° oxygen consumption was almost complete and remained so when the residence time was reduced by small steps (12·5%) down to 17 seconds. A sudden reduction from 40 to 30 seconds stopped the reaction.

Analyses of products obtained at 265° with and without cool flames are given in Table IX.

TABLE IX.

Products of reaction of 2 : 2 : 1 C_6H_{12}–O_2–N_2 *mixture at* 265° (40-secs. *residence*).

	Yields based on oxygen input.			Yields based on oxygen consumption.		
		Without cool flames.	With cool flames.		Without cool flames.	With cool flames.
Carboxyl	4·3	5·4	4·2	5·95	5·75	4·9
Carbonyl	22·85	27·9	18·6	31·65	29·6	21·8
Formaldehyde	4·0	3·9	4·6	5·6	4·2	5·4
Unsaturation	13·6	13·1	13·1	18·85	13·9	15·4
Peroxides (*a*)	2·5	4·1	1·35	3·5	4·35	1·6
(*b*) (i)	0·95	2·65	0·5	1·3	2·8	0·6
(ii)	1·45	0·8	0·95	2·0	0·85	1·1
CO	23·1	29·05	29·6	32·0	30·9	34·8
CO_2	4·6	4·2	3·55	6·4	4·45	4·2
Olefins	5·2	3·55	6·55	8·1	3·75	7·8
O_2, unconsumed	27·85	5·9	14·8	—	—	—
O_2, accounted for	99·4	89·7	85·9	—	—	—

The second of the runs without cool flames was made just before the one with them, but the other experiment was made on another occasion. As there were substantial differences in oxygen consumption in the three experiments, yields are calculated on the basis of oxygen consumption as well as of oxygen input. Allowance being made for evident variability, it seems clear that when cool flames are propagated less peroxidic material survives and the yields of acids and carbonyl compounds (but not formaldehyde) are reduced without corresponding increase in the yield of oxides of carbon.

As compared with the 1 : 1 : 2 mixture at 300° there are improved yields of all condensed products except peroxides. The difference in the latter may be attributed to the long residence times employed at the lower temperature.

We are indebted to the Distillers Company Limited for sponsoring this work and for the supply of methyl*cyclo*pentane. We have also had the advantage of several discussions with members of the Company's Research and Development Department concerning points of detail.

DEPARTMENT OF CHEMICAL ENGINEERING AND APPLIED CHEMISTRY,
IMPERIAL COLLEGE, S. KENSINGTON, LONDON, S.W.7. [*Received, May 30th,* 1950.]

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124. *The Reactions of Metallic Salts of Acids with Halogens. Part I. The Reaction of Metal Trifluoroacetates with Iodine, Bromine, and Chlorine.*

By R. N. HASZELDINE.

Silver, sodium, potassium, mercuric, lead, and barium trifluoroacetates react with iodine to give trifluoroiodomethane. The interaction of the silver salt and bromine and chlorine yields bromo- and chloro-trifluoromethane.

Trifluoroiodomethane and heptafluoroiodopropane have also been prepared by pyrolysis of trifluoroacetyl iodide and heptafluorobutyryl iodide in the presence of iodine.

TRIFLUOROIODOMETHANE has been shown to be a valuable source of trifluoromethyl radicals, some of the reactions of which have already been described (*e.g.*, Haszeldine, *J.*, 1949, 2856; *Nature*, 1950, **165**, 152; Emeléus and Haszeldine, *J.*, 1949, 2948, 2953; Bennett, Brandt, Emeléus, and

Haszeldine, *Nature*, 1950, **166**, 225). Trifluoroiodomethane has hitherto been prepared from carbon tetraiodide and iodine pentafluoride and, although it can be so obtained in excellent yield, the reaction must be carefully controlled and, furthermore, elementary fluorine or chlorine trifluoride is required for the preparation of the iodine pentafluoride (Haszeldine, *J.*, 1950, 3037). Alternative routes to the synthesis of trifluoroiodomethane and other fluoro-iodides have therefore been examined, and a very convenient synthesis may now be effected by the interaction of metal trifluoroacetates and iodine :

$$CF_3{\cdot}CO_2M + I_2 \longrightarrow CF_3I + MI + CO_2$$

$$(CF_3{\cdot}CO_2)_2M' + 2I_2 \longrightarrow 2CF_3I + M'I_2 + 2CO_2$$

(see Haszeldine, *Nature*, 1950, **166**, 192, for preliminary communication).

Sodium (or potassium) trifluoroacetate is now commercially available, and may be prepared without recourse to elementary fluorine. When this salt is heated with excess of iodine at atmospheric pressure, much of the iodine is lost by sublimation, and decarboxylation with simultaneous iodination is incomplete. Thermal decomposition of the sodium trifluoroacetate also occurs and yields trifluoroacetyl fluoride and trifluoroacetic anhydride. In a simple pressure vessel, both sodium and potassium trifluoroacetates give trifluoroiodomethane in good yield.

Other salts of trifluoroacetic acid have been examined. The barium, lead, and mercuric salts react in an analogous manner to the sodium and potassium salts. In all instances it is essential that the metal trifluoroacetate and the iodine should be dry, otherwise trifluoroacetic acid is formed by the reaction

$$6CF_3{\cdot}CO_2M + 3I_2 + 3H_2O \longrightarrow 6CF_3{\cdot}CO_2H + 5MI + MIO_3$$

For this reason the hygroscopic barium and lead salts and the mercuric salt, which must be dehydrated, are unsuitable for general use.

Silver trifluoroacetate is readily prepared from the sodium salt, is stable, non-deliquescent, and does not form a hydrate. Furthermore, the interaction of this salt and iodine, which can be carried out at atmospheric pressure and moderate temperature in simple glass apparatus, gives high yields of the fluoroiodide, and forms the most convenient method for the laboratory synthesis of trifluoroiodomethane.

The interaction of silver trifluoroacetate and chlorine takes place at room temperature and yields chlorotrifluoromethane : similarly the silver salt and bromine react at moderate temperature to give bromotrifluoromethane in equally good yield. The conversion of a fluoro-acid $R{\cdot}CO_2H$ into RX is thus readily achieved, and this enables the conversion of fluoro-iodides into fluoro-acids (Haszeldine, *Nature*, 1950, **166**, 192) to be reversed :

$$\begin{array}{ccc} CF_3{\cdot}[CF_2]_n{\cdot}I & \xrightarrow{C_2H_2} & CF_3{\cdot}[CF_2]_n{\cdot}CH{:}CHI \\ \uparrow{\scriptstyle I_2} & & \downarrow{\scriptstyle KMnO_4} \\ CF_3{\cdot}[CF_2]_n{\cdot}CO_2Ag & \longleftarrow & CF_3{\cdot}[CF_2]_n{\cdot}CO_2H \end{array}$$

The well-known general reaction of silver salts of acids with halogens, due to Simonini (*Monatsh.*, 1892, **13**, 320), has been extensively applied (for a recent review see Kleinberg, *Chem. Reviews*, 1947, **40**, 381). When an equivalent of the silver salt of an acid $R{\cdot}CO_2H$ is treated with two or more equivalents of halogen, the compound $R{\cdot}CO_2X$ is formed (Birckenbach, Goubeau, and Berninger, *Ber.*, 1932, **65**, 1339; Bockemüller and Hoffmann, *Annalen*, 1935, **519**, 165). The decomposition of $R{\cdot}CO_2X$ (X = Cl or Br) gives RX and carbon dioxide, and the reaction of silver trifluoroacetate with halogens (X = Cl, Br, or I) appears to be in accord with this general reaction. Oldham and Ubbelohde (*J.*, 1941, 368) have shown that the thermal decomposition of iodine compounds $I(O{\cdot}COR)_3$ yields the ester, alkyl iodide, carbon dioxide, and iodine. The interaction of equivalent quantities of silver acetate and iodine has been investigated by Simonini (*loc. cit.*) and by Birnbaum (*Annalen*, 1869, **152**, 111), and yields methyl acetate (50—70%) and acetic acid, not methyl iodide. Trifluoromethyl trifluoroacetate has not yet been isolated as a product of the reaction of silver trifluoroacetate and iodine.

Swarts (*Anal. Soc. Fis. Quim.*, 1929, **27**, 683) investigated the reaction of silver trifluoroacetate with iodine in benzene solution, and found that it was represented by the equation

$$2CF_3{\cdot}CO_2Ag + 2I_2 + 2C_6H_6 \longrightarrow (CF_3{\cdot}CO)_2O + H_2O + AgI + C_6H_5I$$

Since, however, the reaction mixture was heated to 60°, it would appear that the products obtained were from a secondary reaction involving iodination of the solvent by the " positive " iodine of iodine trifluoroacetate and decomposition of the latter compound. Reactions carried out in solution, and the degradation of mono- and di-carboxylic fluoro-acids to the iodo-, bromo-, and chloro-compounds, will be described shortly. An alternative, but less convenient, method for the preparation of trifluoroiodomethane from trifluoroacetic acid is by the pyrolysis of the acetyl iodide. The acyl iodides of perfluoro-aliphatic acids have not yet been described, since attempts by Simons and Ramler (*J. Amer. Chem. Soc.*, **1943**, **65**, 389) to prepare trifluoroacetyl iodide by interaction of barium trifluoroacetate and phosphorus tri-iodide failed. As was predicted by these authors, however, the acyl chloride and anhydrous hydrogen iodide react to give the acyl iodide and hydrogen chloride. The reaction appears to be general and heptafluorobutyryl iodide was prepared from heptafluorobutyryl chloride.

The marked effect of fluorine on the boiling point of a compound is illustrated by the comparison of the fluoroacyl halides with their hydrocarbon analogues shown in the table below.

	B.p.		B. p.	Δ B. p.
$CF_3 \cdot COF$ [1]	−59°	$CH_3 \cdot COF$	20·5°	79·5°
$CF_3 \cdot COCl$ [2]	−27	$CH_3 \cdot COCl$	51·5	78·5
$CF_3 \cdot COBr$ [2]	− 5	$CH_3 \cdot COBr$	76·5	81·5
$CF_3 \cdot COI$ [4]	23	$CH_3 \cdot COI$	105	82
$C_3F_7 \cdot COCl$ [3]	39	$C_3H_7 \cdot COCl$	101·5	72·5
$C_3F_7 \cdot COI$ [4]	77·5	$C_3H_7 \cdot COI$	147	69·5

[1] Swarts, *Bull. Acad. Sci. roy. Belg.*, 1922, **8**, 343. [2] Simons and Ramler, *loc. cit.* [3] Haszeldine, *J.*, 1950, 2789. [4] Present communication.

Trifluoroacetyl iodide gave some hexafluoroethane on passage through a heated platinum tube, and the formation of this compound indicated that the decomposition probably proceeded *via* trifluoromethyl radicals; no trifluoroiodomethane was isolated. When pyrolysed in a stream of iodine, however, the trifluoromethyl radicals gave trifluoroiodomethane in low yield. Rapid cooling of the exit gases was used to reduce the amount of hexafluoroethane formed. Pyrolysis of heptafluorobutyryl iodide in a stream of iodine similarly gave heptafluoroiodopropane, a compound previously prepared from trifluoroiodomethane and tetrafluoroethylene (Haszeldine, *loc. cit.*).

Experimental.

Preparation of Silver Trifluoroacetate.—Sodium trifluoroacetate was dissolved in the minimum amount of water and added to a concentrated aqueous solution of silver nitrate. The solution was filtered to remove traces of silver chloride and extracted with ether overnight. This was sufficient to remove most of the silver trifluoroacetate, but a further small quantity was obtained by concentration of the aqueous solution on a steam-bath until on cooling a few crystals could be observed, followed by further extraction with ether. The ethereal extracts were evaporated to dryness on the steam-bath, then powdered, and the drying completed in a vacuum-desiccator over silica gel.

Silver trifluoroacetate was also prepared from the free acid by addition of silver oxide to a 50% aqueous solution and evaporation to dryness *in vacuo*. A slight excess of silver oxide did not affect the subsequent reactions of the silver salt.

Interaction of Silver Trifluoroacetate and Iodine.—In a typical experiment, silver trifluoroacetate (100 g.) was intimately mixed with excess of iodine (300 g.) in a 2-l. Pyrex flask fitted with wide-bore air- and water-condensers and connected by wide-bore rubber tubing to two traps cooled by liquid air. The reaction was initiated by application of a free flame at the upper edge of the mixture. Fumes of iodine were evolved, and a stream of faintly pink gas could be observed passing through the condensers. The reaction was readily controlled by intermittent application of the flame and was allowed to spread slowly throughout the whole reaction mixture. Excessive heating led to a too rapid gas evolution with loss of iodine into the condensers, and for this reason the use of a heating bath is to be recommended only for work on a small scale.

The traps contained carbon dioxide, iodine, and trifluoroiodomethane, and the last was easily separated by distillation *in vacuo*; alternatively, the carbon dioxide and iodine were removed by washing with dilute aqueous alkali. The fluoro-iodide (81 g., 91%), b. p. −22°, prepared by this method was identical with that obtained from carbon tetraiodide and iodine pentafluoride (b. p. −22·5°) (Found: I, 64·6%; *M*, 196. Calc. for CF_3I: I, 64·8%; *M*, 196). Yields of 89—94% were consistently obtained.

When equimolar amounts of silver trifluoroacetate and iodine were mixed and heated as above, the yield of trifluoroiodomethane was reduced to 80—84%. No other products were isolated, and it is believed that the decrease in yield is due not to side reactions but to mechanical difficulties such as the incomplete mixing of the iodine and silver salt.

Interaction of Silver Trifluoroacetate and Bromine.—To silver trifluoroacetate (11 g.) in four Pyrex tubes cooled in liquid air was added bromine (16 g.). The tubes were then evacuated and sealed. On

warming to room temperature, a reaction was apparent and silver bromide was deposited. The reaction was completed by warming the mixture to 50° for 2 hours. The volatile products were washed with aqueous alkali, and distillation gave bromotrifluoromethane (6·5 g., 88%) (Found: Br, 53·2%; *M*, 149. Calc. for $CBrF_3$: Br, 53·7%; *M*, 149), b. p. −58°. Banks, Emeléus, Haszeldine, and Kerrigan (*J.*, 1948, 2188) report b. p. −57·8°. The reaction can also be carried out at atmospheric pressure by heating a mixture of silver trifluoroacetate and bromine on a water-bath.

Interaction of Silver Trifluoroacetate and Chlorine.—Silver trifluoroacetate (11 g.) and chlorine (6·5 g.) were sealed in four tubes and allowed to warm to room temperature. A vigorous reaction ensued and silver chloride was formed. The volatile products of reaction were washed with alkali, and on fractionation yielded chlorotrifluoromethane (4·7 g., 90%) (Found: *M*, 104·5. Calc. for $CClF_3$: *M*, 104·5), b. p. −82°.

Reaction of Sodium and Potassium Trifluoroacetate with Iodine.—Sodium and potassium trifluoroacetate were dried *in vacuo* on a water-bath before use. Vigorous heating with a free flame was needed to bring about the reaction of the sodium salt (27·2 g.) and iodine (100 g.) at atmospheric pressure. Much of the iodine sublimed and distilled from the salt before reaction occurred. The products of reaction were trifluoroiodomethane (3·9 g., 10%), carbon dioxide, carbonyl fluoride, silicon tetrafluoride, trifluoroacetyl fluoride (b. p. *ca.* −60°), and trifluoroacetic anhydride (b. p. 40°). By reaction of the last two compounds with aqueous alkali, neutralisation to bromothymol-blue with dilute sulphuric acid, and evaporation to dryness followed by extraction with absolute ethanol, a total of 6 g. (22%) of sodium trifluoroacetate was recovered.

When potassium trifluoroacetate (30·5 g.) was heated at atmospheric pressure with a large excess of iodine (500 g.), the yield of trifluoroiodomethane was 40%.

Sodium trifluoroacetate (13·6 g.) heated to 270° in a sealed tube with iodine (70 g.) gave a 58% yield of the fluoro-iodide.

Sodium trifluoroacetate (27·2 g.) was mixed with iodine (200 g.) in a 100-ml. stainless-steel autoclave and heated during 4 hours to a maximum temperature of 280°. Trifluoroiodomethane (24·1 g.) was isolated in 61% yield. The potassium salt under identical conditions gave a 55% yield of the fluoro-iodide. It may not be necessary to use a temperature as high as 280°.

Reaction of Barium, Mercuric, and Lead Trifluoroacetates with Iodine.—These salts were first described by Swarts (*Bull. Soc. chim. Belg.*, 1939, **48**, 176). Barium trifluoroacetate was prepared by addition of 60% aqueous trifluoroacetic acid to an equivalent amount of barium hydroxide, and evaporation to dryness on a water-bath. Dehydration was completed in a vacuum-desiccator over phosphoric anhydride, with pumping, for several weeks. Mercuric and lead trifluoroacetates were similarly prepared from mercuric and lead oxides and 30% trifluoroacetic acid. Reaction with iodine was effected in an autoclave as described for sodium and potassium trifluoroacetates. The barium, mercuric, and lead salts were heated to 280°, 250°, and 250° to give 32, 35, and 26% yields of trifluoroiodomethane, respectively.

Trifluoroacetyl Iodide and Heptafluorobutyryl Iodide.—Trifluoroacetyl chloride (26 g.) was prepared from sodium trifluoroacetate and phosphorus trichloride, sealed in 12 tubes with anhydrous hydrogen iodide (50 g.), and heated to 120° for 8 hours. The products of reaction were given a preliminary distillation through a series of cooled traps to remove hydrogen chloride and hydrogen iodide, followed by fractionation to give *trifluoroacetyl iodide* (28 g., 62%) (Found: I, 56·9%; *M*, 222. C_2F_3OI requires I, 56·7%; *M*, 224), a liquid, b. p. 23°, which fumes in air.

Heptafluorobutyryl iodide (5·1 g., 57%) (Found: C, 15·1; I, 39·4%; *M*, 318. C_4F_7OI requires C, 14·8; I, 39·2%; *M*, 324), b. p. 77—78°, n_D^{25} 1·353, was similarly prepared from heptafluorobutyryl chloride (6·4 g.) and anhydrous hydrogen iodide (13 g.).

Pyrolysis of Trifluoroacetyl Iodide and Heptafluorobutyryl Iodide.—The apparatus consisted of a cylindrical Pyrex tube containing iodine and heated electrically, through which a stream of nitrogen was passed. Iodine vapour was thereby carried through a wide-bore exit tube and into a platinum tube 30″ long and of ½″ internal diameter heated to 550—600°. Once it had been established that iodine was flowing through the tube, trifluoroacetyl iodide, slightly diluted by nitrogen, was added through a T-piece and mixed with the iodine before entering the tube. The optimum conditions were not investigated. On leaving the furnace, the exit gases were cooled as rapidly as possible by a series of wide-bore traps cooled in liquid air. Trifluoroacetyl iodide (8 g.), added during 2 hours with a nitrogen dilution of 4 l./hr., gave 15, 20, and 22% yields of trifluoroiodomethane in consecutive experiments. Trifluoroacetyl iodide, pyrolysed alone at 550°, gave no trifluoroiodomethane; hexafluoroethane (10%) was detected and some trifluoroacetyl iodide was recovered unchanged.

Similarly, heptafluorobutyryl iodide (4·8 g.), added at 2 g./hr., gave heptafluoroiodopropane (16%), b. p. 40°, *M* 296, identical with the material prepared earlier from trifluoroiodomethane and tetrafluoroethylene.

Professor A. L. Henne of Ohio State University reports (private communication) that he has independently prepared trifluoroiodomethane from silver trifluoroacetate and iodine.

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UNIVERSITY CHEMICAL LABORATORY,
PEMBROKE STREET, CAMBRIDGE.

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125. *The Reactions of Fluorocarbon Radicals. Part IV. The Synthesis of 3 : 3 : 3-Trifluoropropyne.*

By R. N. Haszeldine.

Interaction of trifluoroiodomethane and acetylene gives mainly 3 : 3 : 3-trifluoro-1-iodopropene, dehydroiodination of which yields 3 : 3 : 3-trifluoropropyne, the first of a new class of compound with perfluoroalkyl groups adjacent to an acetylenic residue. The hydrogen atom is acidic, and copper, silver, and mercuric trifluoromethylacetylides have been prepared. The last compound is a stable low-melting solid. Oxidation of the fluoroalkyne affords trifluoroacetic acid, and hydrogenation and chlorination give 1 : 1 : 1-trifluoropropane and 1 : 1 : 2 : 2-tetrachloro-3 : 3 : 3-trifluoropropane respectively.

In order to study the effect of strongly electronegative fluorocarbon groups on organic functional groups, compounds of the type RX are required where R is the fluorocarbon group linked directly to X, a potentially reactive group such as $\cdot CO_2H$, $\cdot OH$, $\cdot CO$, $\cdot CHO$, $\cdot NH_2$, $\cdot C{\equiv}CH$, and $\cdot MgX$. The syntheses of fluoroalkyl iodides, RI, have enabled methods to be developed for the preparation of compounds of the type $R\cdot CO_2H$, $R\cdot MgX$ (Haszeldine, *J.*, 1950, 2789; *Nature*, in the press), $R\cdot OH$, and $R\cdot NH_2$. The present communication is concerned with the synthesis of a compound of the type $R\cdot C{\equiv}CH$, where $R = CF_3$.

In Part II (*J.*, 1950, 3037) it was shown that trifluoroiodomethane and acetylene underwent an addition-polymerisation to give the compounds $CF_3\cdot[CH{:}CH]_n\cdot I$ ($n = 1$ and 2). Trifluoropropyne (trifluoromethylacetylene) has now been synthesised from 3 : 3 : 3-trifluoro-1-iodopropene by dehydroiodination :

$$CF_3\cdot CH{:}CHI \xrightarrow{-HI} CF_3\cdot C{\equiv}CH$$

this was most conveniently effected by powdered potassium hydroxide, sodamide and alcoholic potassium hydroxide being less satisfactory. The fluoroalkyne (first described in *Nature*, 1950, **165**, 152) is a colourless gas, b.p. −48°, and the effect of structure on the boiling points of 1 : 1 : 1-trifluoropropane derivatives is illustrated in the following table.

Compound.	B. p.	Compound.	B. p.
$CF_3\cdot CH_2\cdot CH_3$	−13°	$CH_3\cdot CH_2\cdot CH_3$	−42°
$CF_3\cdot CH{:}CH_2$ *	−22	$CH_3\cdot CH{:}CH_2$	−48
$CF_3\cdot C{\equiv}CH$	−48	$CH_3\cdot C{\equiv}CH$	−23

* Haszeldine, *J.*, 1950, 3037. Henne and Waalkes, *J. Amer. Chem. Soc.*, 1946, **68**, 496, report b. p. −17° to −19° and Robbins, *J. Pharmacol.*, 1946, **86**, 197, reports b. p. −24°.

The difference in boiling point of trifluoropropane and trifluoropropene is 9°, a value comparable with that for propane and propylene (6°). On passing from trifluoropropane to trifluoropropyne, however, a *decrease* in boiling point of 35° is found as compared with an increase of 20° for propane to propyne. In the butane series, Henne and Finnegan (*J. Amer. Chem. Soc.*, 1949, **71**, 298) have attributed the decrease in boiling point of 50° on passing from $CF_3\cdot CH_2\cdot CH_2\cdot CF_3$ (b. p. 25°) *via* $CF_3\cdot CH{:}CH\cdot CF_3$ (b. p. 33°) to $CF_3\cdot C{\equiv}CCF_3$ (b. p. −25°) to the absence of hydrogen bonding.

That the compound obtained by dehydroiodination of 3 : 3 : 3-trifluoro-1-iodopropene was actually trifluoromethylacetylene was proved by the following reactions. Oxidation with alkaline permanganate gave trifluoroacetic acid, hydrogenation gave the known compound $CF_3\cdot CH_2\cdot CH_3$, and addition of chlorine gave the hitherto unknown compound 1 : 1 : 2 : 2-tetrachloro-3 : 3 : 3-trifluoropropane, with physical properties similar to its known $C_3HF_3Cl_4$ isomers as shown in the second table. The close similarity in the physical properties of other highly halogenated propanes is also revealed in this table. It will be noted that the freezing or melting point is the property most sensitive to structural isomerism, and that compounds containing hydrogen are liquids which tend to give glasses on cooling. The parallelism between melting point and the asymmetrical distribution of fluorine and chlorine in chlorofluorocompounds has been noted by Henne, Renoll, and Leicester (*J. Amer. Chem. Soc.*, 1939, **61**, 938).

Compound.	B. p.	n_D.	F. p.	Compound.	B. p.	n_D.	F. p.
			$C_2HF_3Cl_4$.				
$CFCl_2{\cdot}CF_2{\cdot}CHCl_2$...	127°	1·4189[25]	—[1]	$CF_3{\cdot}CHCl{\cdot}CCl_3$ ...	125·1°	1·4180[24]	—[4]
$CF_2Cl{\cdot}CHCl{\cdot}CFCl_2$	128·7	1·4157[25]	Glass[2]	$CF_3{\cdot}CCl_2{\cdot}CHCl_2$ ...	126—126·5	1·4195[25]	—[5]
$CF_2Cl{\cdot}CFCl{\cdot}CHCl_2$	129·8	1·4197[20]	Glass[2]				
			$C_2F_3Cl_3$.				
$CFCl_2{\cdot}CF_2{\cdot}CCl_3$ ...	154·5	1·4394[20]	< −80°[3]	$CFCl_2{\cdot}CFCl{\cdot}CFCl_2$	154·7	1·4387[20]	Glass[7]
	152—154	1·4389[20]	—[6]	$CF_2Cl{\cdot}CFCl{\cdot}CCl_3$...	153·3	1·4392[20]	−14·8[8]
	155·5—157	1·4399[25]	55—56[1]	$CF_2Cl{\cdot}CCl_2{\cdot}CFCl_2$	152·3	1·4396[20]	− 4·9[8]
				$CF_3{\cdot}CCl_2{\cdot}CCl_3$	153·1	—	109[8,5]
			$C_2F_4Cl_4$.				
$CCl_3{\cdot}CF_2{\cdot}CF_2Cl$ ...	112·0—112·5	1·3961[20]	—[9]	$CF_2Cl{\cdot}CFCl{\cdot}CFCl_2$	112·5	1·3960[20]	−58[10]
				$CF_2Cl{\cdot}CCl_2{\cdot}CF_2Cl$	112·0	1·3958[20]	−42·9[8]
	114·5	1·3974[25]	—[1]	$CF_3{\cdot}CFCl{\cdot}CCl_3$ ...	112·5	1·4002[20]	12·1[10]
$CFCl_2{\cdot}CF_2{\cdot}CFCl_2$...	112·5—115	1·3980[25]	—[1]	$CF_3{\cdot}CCl_2{\cdot}CFCl_2$ ...	112·4	—	41·7[9]

[1] Coffman, Cramer, and Rigby, *J. Amer. Chem. Soc.*, 1949, **71**, 979. [2] Henne and Renoll, *ibid.*, 1939, **61**, 2489. [3] Henne and Ladd, *ibid.*, 1938, **60**, 2491. [4] McBee, Truchan, and Bolt, *ibid.*, 1948, **70**, 2023. [5] This paper. [6] Henne and Renoll, *J. Amer. Chem. Soc.*, 1937, **59**, 2434. [7] Henne and Newby, *ibid.*, 1948, **70**, 130. [8] Henne and Whaley, *ibid.*, 1942, **64**, 1157. [9] McBee, Henne, Hass, and Elmore, *ibid.*, 1940, **62**, 3340. [10] Henne and Haeckl, *ibid.*, 1941, **63**, 3476.

A hydrogen atom on a carbon atom adjacent to a perfluoroalkyl group is resistant to halogenation, and the chlorination of $CF_3{\cdot}CHCl{\cdot}CCl_3$ or $CF_3{\cdot}CH_2{\cdot}CCl_3$, for example, is achieved only with difficulty, even on irradiation with ultra-violet light. The compound obtained by addition of two molecules of chlorine to trifluoromethylacetylene contains a hydrogen atom on a carbon atom once removed from the trifluoromethyl group, and further chlorination was readily achieved in ultra-violet light of moderate intensity. The product, $CF_3{\cdot}CCl_2{\cdot}CCl_3$, was identical with that obtained on prolonged chlorination of the hydrogenated acetylene, and also with the compound prepared by complete chlorination of a known specimen of 1 : 1 : 1-trifluoropropane, obtained by interaction of trifluoroiodomethane and ethylene (Haszeldine, *J.*, 1949, 2856). Henne and Whaley have also prepared $CF_3{\cdot}CCl_2{\cdot}CCl_3$ (see table) and report the same physical properties. The reactions described above establish the carbon skeleton and presence of a triple bond and a trifluoromethyl group.

The hydrogen atom of trifluoromethylacetylene is, as expected, markedly acidic, and can be replaced by metals to yield fluoroacetylides. Treatment with ammoniacal cuprous chloride or silver nitrate affords copper or silver trifluoromethylacetylide, both derivatives being soluble in organic solvents. Mercuric trifluoromethylacetylide is obtained as a low-melting crystalline solid when trifluoromethylacetylene is treated with alkaline potassium mercuri-iodide. The fluoroacetylides are reconverted into the fluoroalkyne when treated with acids, thus showing that they are true acetylides and not addition products. This is of particular importance for the mercury compound, since it is conceivable that addition of mercury salts across the triple bond could also occur.

It is noteworthy that the acetylides formed from trifluoromethylacetylene, unlike those formed from acetylene, are not of complex composition and do not retain water or groups or anions which were linked to the metal in the original salt. Trifluoromethylacetylene yields much more complex products of variable composition when treated with neutral or acid solutions of copper, silver, or mercury salts. These products are insoluble in water and many organic solvents, and do not yield trifluoromethylacetylene quantitatively with acid.

When mercuric trifluoromethylacetylide is treated with iodine, a compound believed to be 3 : 3 : 3-trifluoro-1-iodopropyne, with a characteristic odour like that of di-iodoacetylene, is produced.

The homologues of trifluoromethylacetylene, $C_2F_5{\cdot}C{\equiv}CH$ and $C_3F_7{\cdot}C{\equiv}CH$, have recently been synthesised (Haszeldine and Leedham, unpublished). The influence of the perfluoroalkyl group on the reactivity of the triple bond in ionic and free-radical addition reactions and on reactions involving the acetylenic hydrogen atom is expected to be marked, and is being investigated.

Experimental.

Preparation of 3 : 3 : 3-*Trifluoro*-1-*iodopropene*.—This compound was prepared by interaction of trifluoroiodomethane and acetylene at 200—220°, and constituted 70—80% of the product. Further examination of the higher-boiling material has revealed the presence of small amounts of *trans*- and possibly *cis*-di-iodoethylene in addition to the compounds previously isolated. The *trans*-isomer (Found :

C, 8·6; H, 0·8; I, 89·7. Calc. for $C_3H_3I_3$: C, 8·6; H, 0·7; I, 90·7%) was recrystallised from aqueous ethanol, giving needles, m.p. 72—73°; Keiser (*Amer. Chem. J.*, 1899, **21**, 265) gives m. p. 73°.

Dehydroiodination of 3 : 3 : 3-*Trifluoro*-1-*iodopropene.*—The fluoroiodopropene (24 g.) was added to a large excess of dried, powdered potassium hydroxide (150 g.) in a 100-ml. flask fitted with a reflux condenser connected *via* rubber tubing to a trap cooled by liquid air. The temperature was gradually raised from 120° to 150° (bath-temp.) during 6 hours, at the end of which most of the olefin had disappeared. The flask was disconnected and heated *in vacuo* for recovery of unchanged 3 : 3 : 3-trifluoro-1-iodopropene (2 g.).

The material which had passed through the reflux condenser during the dehydroiodination was transferred to a vacuum system where it was fractionated. A small amount (0·1 g.) of entrained 3 : 3 : 3-trifluoro-1-iodopropene was thereby removed from the 3 : 3 : 3-*trifluoropropyne* (6·6 g., 70%) (Found : C, 39·4; H, 1·2; F, 60·1%; *M*, 94. C_3HF_3 requires C, 38·3; H, 1·1; F, 60·6%; *M*, 94), b. p. −48° to −46°. The analysis of the fluoroalkyne for carbon and hydrogen was somewhat difficult since it tended to explode and flash along the combustion tube when mixed with oxygen and heated; a slow stream of the organic compound with a large excess of oxygen was finally used for combustion.

In repeat experiments, and with quantities of fluoroiodopropene up to 30 g., 68—75% yields of trifluoromethylacetylene were obtained. The dehydroiodination could also be effected by heating small amounts of 3 : 3 : 3-trifluoro-1-iodopropene with powdered potassium hydroxide at 120—180° in Carius tubes.

Properties of 3 : 3 : 3-*Trifluoropropyne.*—The fluoroalkyne is a colourless gas, with an odour like that of acetylene, whose vapour pressure determined over the range −135° to −60° is represented by the equation $\log_{10} p = 7{\cdot}8808 - 1124/T$, whence the calculated boiling point is −48·3°. Trouton's constant is 22·8, and the latent heat of vaporisation is 5140 cals./mole.

Copper derivative. Trifluoromethylacetylene (0·1 g.) was shaken in a sealed tube with a filtered solution of cuprous chloride in ammonium hydroxide. An immediate khaki-coloured precipitate was produced which, if left overnight, darkened to a brown solid. A freshly prepared specimen of the copper derivative was removed by filtration, washed with water, and dried *in vacuo* over silica gel. When heated gently, *cuprous trifluoromethylacetylide* (Found : C, 22·8; F, 36·1; Cu, 40·8. C_3F_3Cu requires C, 23·0; F, 36·4; Cu, 40·6%) slowly decomposed; rapid heating brought about the vigorous decomposition of larger quantities with occasionally a slight explosion.

Analysis for carbon was carried out by carefully heating a small specimen in a standard combustion tube, and fluorine was determined after sodium fusion. Analysis for copper was most conveniently effected after dissolution and warming of the acetylide in dilute nitric acid; identification of the evolved gas as trifluoromethylacetylene proved that the copper derivative was a true acetylide. Copper trifluoromethylacetylide was soluble in alcohol and ether, and was not contaminated by chlorine-containing compounds.

Silver derivative. An immediate white precipitate was produced when trifluoromethylacetylene was shaken with ammoniacal silver nitrate. The precipitate, removed by filtration and washed with water, was shown to be *silver trifluoromethylacetylide* (Found : C, 17·4; F, 27·9; Ag, 54·1. C_3F_3Ag requires C, 17·9; F, 28·4; Ag, 53·7%). Analysis for silver was carried out after warming with dilute nitric acid and removal and identification of the evolved trifluoromethylacetylene. Fluorine was determined after sodium fusion, and carbon by careful combustion in oxygen. Silver trifluoromethylacetylide is a white solid which changes to a fawn colour when kept in a desiccator or on exposure to light. When heated rapidly it decomposes violently, but a steady decomposition occurs when it is heated slowly and metallic silver is left; this gives an alternative method of analysis (Found : Ag, 54·5%).

When trifluoromethylacetylene is shaken with a neutral or slightly acid silver nitrate solution, the white precipitate so obtained is much more complex; it is only slightly soluble in organic solvents and contains traces of apparently combined water and of anions from the aqueous solution.

Mercuric derivative. Mercuric chloride (33 g.) and potassium iodide (82 g.) were dissolved in water (80 ml.) and 10% potassium hydroxide (60 ml.) was added. After filtration, a portion of the clear yellow solution (10 ml.) was shaken with trifluoromethylacetylene (0·4 g.) in a sealed tube. A colourless oil was immediately formed as a lower layer, and to remove inorganic salts this was thoroughly washed with water by centrifugation and decantation. The oil, which had a strong odour of trifluoromethylacetylene, was transferred to a short-path still and heated to 60° under 400 mm. The crude acetylide crystallised on the cold finger of the short-path still in the form of needles, m.p. 39—41°. Further sublimation at atmospheric pressure gave *mercuric trifluoromethylacetylide* (Found : C, 18·6; F, 29·1; Hg, 51·4. C_6F_6Hg requires C, 18·6; F, 29·5; Hg, 51·9%) as a white crystalline solid, m. p. 44—45°, which did not contain traces of iodine or chlorine.

In further experiments, the acetylide, after thorough washing with water, was dissolved in ether, removal of which gave the crude crystalline acetylide, m. p. 39—41°. The use of a large excess of potassium iodide in making the mercuri-iodide reduced the yield of the acetylide. In some instances the acetylide was precipitated as a solid, and it was found preferable to melt the compound by gentle warming so that it could be washed efficiently with water. Mercuric trifluoromethylacetylide liberated trifluoromethylacetylene when warmed with mineral acids. When the theoretical amount of iodine dissolved in hexane was added to the acetylide, the colour was immediately reduced in intensity. Evaporation of a portion of the solution gave a residue which contained mercuric iodide and had an odour very similar to the characteristic odour of di-iodoacetylene and $-C{\equiv}CI$ compounds in general. The isolation of this compound, believed to be 3 : 3 : 3-trifluoro-1-iodopropyne, in a pure state was not attempted.

Oxidation of 3 : 3 : 3-*Trifluoropropyne.*—The fluoroalkyne (1 g.) was readily oxidised by alkaline potassium permanganate to give trifluoroacetic acid (cf. Haszeldine, *J.*, 1950, 2789, and Part II, *loc. cit.*).

The acid was not isolated as such but was esterified and converted into the amide (0·25 g.), m. p. 74°, for identification.

Hydrogenation of 3 : 3 : 3-*Trifluoropropyne.*—The alkyne (4·0 g.) was heated with hydrogen (80 atm.) to a final temperature of 80° in the presence of Raney nickel. The product was 1 : 1 : 1-trifluoropropane (3·9 g.) (Found: *M*, 98. Calc.: *M*, 98), b. p. −12°. The hydrogenated material showed no reaction with chlorine in the dark at 40° and was not unsaturated. When it was sealed with excess of chlorine in a silica tube and exposed to ultra-violet radiation, a slow reaction occurred and after 3 days 1 : 1 : 1 : 2 : 2-pentachloro-3 : 3 : 3-trifluoropropane (3·7 g.) (Found: Cl, 64·8. Calc. for $C_3Cl_5F_3$: Cl, 65·6%), m. p. 108—109°, b. p. (micro) 155° (cf. table above), and a mixture of 1 : 1-dichloro-3 : 3 : 3-trifluoropropane and 1 : 1 : 1-trichloro-3 : 3 : 3-trifluoropropane were isolated. A specimen of 1 : 1 : 1-trifluoropropane prepared from 1 : 1 : 1-trifluoro-3-iodopropane (Haszeldine, *loc. cit.*) reacted in an analogous manner and gave a specimen of the pentachlorotrifluoropropane whose m. p. was not changed on admixture with the compound obtained by chlorination of the hydrogenated trifluoromethylacetylene.

Addition of Chlorine to Trifluoromethylacetylene.—Trifluoromethylacetylene (2·0 g.) was sealed in a tube with a slight excess of chlorine (3·1 g.), and the mixture allowed to warm to room temperature. After 24 hours at 50° in the dark, the tube was opened and the contents were given a preliminary distillation to remove material with b. p. <0°; no alkyne or hydrogen chloride, but only a trace of chlorine was recovered. The material, b. p. >0°, was distilled at atmospheric pressure to give: (1) a small amount (0·1 g.) of liquid, b. p. 55—60°, n_D^{25} 1·366, which was probably $CF_3{\cdot}CCl{:}CHCl$ (Henne, Whaley, and Stevenson, *J. Amer. Chem. Soc.*, 1941, 3478, report b. p. 53·7°, n_D^{20} 1·3670); (2) 1 : 1 : 2 : 2-*tetrachloro*-3 : 3 : 3-*trifluoropropane* (3·6 g.; 72%) (Found: C, 15·8; H, 0·7; Cl, 60·1. $C_3HCl_4F_3$ requires C, 15·3; H, 0·4; Cl, 60·2%), b. p. 126—126·5°, n_D^{25} 1·4195; (3) still residue (1·0 g.).

The tetrachlorotrifluoropropane was mixed with a 20% excess of chlorine in a Pyrex tube and exposed to ultra-violet radiation (*i.e.*, of wave-length >2900 A.) (chlorination of a mixture of $CF_3{\cdot}CH_2{\cdot}CHCl_2$ and $CF_3{\cdot}CH_2{\cdot}CCl_3$ proceeded extremely slowly under such conditions); after 4 hours the excess of chlorine was allowed to evaporate and the contents of the tube were taken up in ether, evaporation of which gave 1 : 1 : 1 : 2 : 2-pentachloro-3 : 3 : 3-trifluoropropane (2·2 g.) (Found: C, 13·5; Cl, 65·3. Calc. for $C_3Cl_5F_3$: C, 13·3; Cl, 65·6%) as a white crystalline solid, purified by sublimation, m. p. 109°, unaltered by admixture with the pentachlorotrifluoropropane prepared by exhaustive chlorination of 1 : 1 : 1-trifluoropropane.

Professor A. L. Henne reports (private communication) that trifluoromethylacetylene has now been prepared from $CF_3{\cdot}CBr{:}CH_2$ and that the b. p. of the compound so obtained confirms that of the compound reported in *Nature* (*loc. cit.*).

UNIVERSITY CHEMICAL LABORATORY,
PEMBROKE STREET, CAMBRIDGE.

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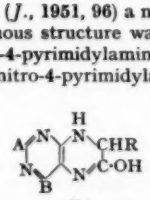
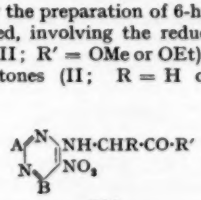
126. *Pteridines. Part II. The Synthesis of Some α-(5-Nitro-4-pyrimidylamino)-ketones and Their Conversion into 7 : 8-Dihydropteridines and Pteridines.*

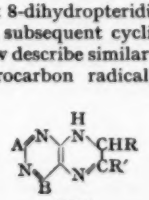
By W. R. BOON and W. G. M. JONES.

Condensation of 4-chloro-5-nitropyrimidines with α-amino-ketones gives α-(5-nitro-4-pyrimidylamino)-ketones, reduction of which provides an unambiguous and useful synthesis of 7 : 8-dihydropteridines and pteridines.

IN Part I (*J.*, 1951, 96) a method for the preparation of 6-hydroxy-7 : 8-dihydropteridines (I) of unambiguous structure was described, involving the reduction and subsequent cyclisation of α-(5-nitro-4-pyrimidylamino)-esters (II; R′ = OMe or OEt). We now describe similar reactions for α-(5-nitro-4-pyrimidylamino)-ketones (II; R = H or a hydrocarbon radical, R′ = a


(I.)


(II.)


(III.)

hydrocarbon radical), which are particularly useful for the preparation of 7 : 8-dihydropteridines of type (III) (cf. Boon, Jones, and Imperial Chemical Industries Ltd., B.P. 635,582). Recently Polonovski, Pesson, and Puister (*Compt. rend.*, 1950, **230**, 2205) have prepared 2-ethoxy-7 : 8-dihydro-4-methyl-6 : 7-diphenylpteridine by a similar route.

Owing to the generally greater tendency of α-amino-ketones than of α-amino-esters to undergo self-condensation, it was not possible to cause the chloronitropyrimidine to react with the free amino-ketone. Good results were obtained, however, by allowing a suspension of the amino-ketone hydrochloride to react with a solution of the chloronitropyrimidine in an inert solvent in the presence of a mild alkali, such as sodium hydrogen carbonate. Thus, 2 : 4-dichloro-5-nitropyrimidine was readily converted into 2-chloro-5-nitro-4-pyrimidylaminoacetone (II; A = Cl, B = R = H, R′ = Me) in 50% yield. Replacement of the second chlorine atom by an amino-, benzylamino-, or diethylamino-group proceeded smoothly, the resulting products being readily hydrogenated over Raney nickel to the corresponding dihydropteridines. Reduction of 2-chloro-5-nitro-4-pyrimidylaminoacetone did not proceed as smoothly as that of the corresponding ethyl 2-chloro-5-nitro-4-pyrimidylaminoacetate (Boon *et al.*, *loc. cit.*): reduction in methanol solution over Raney nickel, at the ordinary temperature, ceased after the absorption of two moles of hydrogen, with the separation of an unstable product analysis of which approximated to that for 4-acetonylamino-2-chloro-5-pyrimidylhydroxylamine. This substance, which was soluble in both acid and alkali, reduced Fehling's solution and was decomposed when warmed. A solution in dimethylformamide absorbed a further mole of hydrogen over Raney nickel but no characterisable product could be isolated. Similarly, no crystalline product could be isolated after similar reduction of 2-chloro-6-methyl-5-nitro-4-pyrimidylaminoacetone.

Condensation of amino-ketones with 4 : 6-dichloro-5-nitropyrimidines was, in general, less satisfactory than that with the 2 : 4-dichloro-5-nitro-compounds, owing, in part, to the smaller difference in reactivity between the two chlorine atoms in the former case and, in part also, to the marked sensitivity of the 6-chloro-5-nitro-4-pyrimidylamino-ketones to moisture. In only one case has a product containing two α-amino-ketone residues been isolated: condensation of 4 : 6-dichloro-5-nitropyrimidine with α-aminodeoxybenzoin yields a mixture of α-(6-chloro-5-nitro-4-pyrimidylamino)benzyl phenyl ketone (II; A = H, B = Cl, R = R′ = Ph) and 5-nitro-4 : 6-di-(α-phenylphenacylamino)pyrimidine (II; A = H, B = NH·CHPh·CO·Ph, R = R′ = Ph). 6-Chloro-5-nitro-4-pyrimidylaminoacetone and the corresponding 2-methyl compound are readily hydrolysed by water to the corresponding 6-hydroxy-compounds, conversion being complete after a short exposure to moist air (which vitiates analysis). By working rapidly, however, it was possible to replace the second halogen atom smoothly by amino- or substituted amino-groups.

4-Chloro-6-ethoxy-2-methyl-5-nitropyrimidine did not react with aminoacetone under the usual conditions, but condensation with glycine methyl ester gave methyl 6-ethoxy-2-methyl-5-nitro-4-pyrimidylaminoacetate.

Oxidation of the dihydropteridines with alkaline permanganate proceeded readily in all cases so far examined. Thus, 4-amino-7 : 8-dihydro-6 : 7-dimethyl-, 4-amino-7 : 8-dihydro-6 : 7-diphenyl-, and 4-diethylamino-7 : 8-dihydro-6 : 7-diphenyl-pteridines gave pteridines identical with those obtained directly by condensation of the appropriate 4 : 5-diaminopyrimidine and α-diketone. In some cases, the required product was more readily obtained by oxidation of the dihydro-compound: *e.g.*, 4 : 5 : 6-triaminopyrimidine and benzil gave only a small yield of pteridine; 2 : 4 : 5-triaminopyrimidine and benzil gave none of the pteridine; and 4 : 5-diamino-2-diethylaminopyrimidine is sensitive to aerial oxidation.

4-Amino-6-diethylamino-5-nitropyrimidine was reduced smoothly over Raney nickel to 4 : 5-diamino-6-diethylaminopyrimidine. In addition to condensation with benzil, noted above, this substance reacted readily with glyoxal, diacetyl, acenaphthenequinone, phenanthraquinone, and furil to give the corresponding pteridines. Condensation with 4 : 4′-dichlorobenzil gave only a low yield of pteridine, and none was obtained from anisil.

Experimental.

Microanalyses are by Drs. Weiler and Strauss.

4-Amino-2-diethylamino-5-nitropyrimidine.—Diethylamine (9 g., 0·13 mol.) was added with cooling to a solution of 4-amino-2-chloro-5-nitropyrimidine (8·75 g., 0·05 mol.) in dioxan (100 c.c.). After 18 hours the diethylamine hydrochloride was filtered off and washed with dioxan. Evaporation of the filtrate to dryness and crystallisation of the residue from aqueous methanol gave *4-amino-2-diethylamino-5-nitropyrimidine* (9·9 g., 87%), m. p. 109—110° (Found: C, 45·9; H, 6·1; N, 33·3. $C_8H_{13}O_2N_5$ requires C, 45·5; H, 6·2; N, 33·2%).

4-Amino-6-diethylamino-5-nitropyrimidine, m. p. 119° (from aqueous methanol) (Found: C, 45·2; H, 6·2; N, 33·4. $C_8H_{13}O_2N_5$ requires C, 45·5; H, 6·2; N, 33·2%), and *4-amino-5-nitro-6-morpholinopyrimidine*, m. p. 182° (from benzene) (Found: C, 42·7; H, 4·9; N, 31·2. $C_8H_{11}O_3N_5$ requires C,

42·7; H, 4·9; N, 31·1%), were obtained similarly in 90% and 75% yield respectively from 4-amino-6-chloro-5-nitropyrimidine.

4-Chloro-6-ethoxy-2-methyl-5-nitropyrimidine.—To a cold solution of 4 : 6-dichloro-2-methyl-5-nitropyrimidine (10 g.) in absolute ethanol there was added, with stirring, a solution of sodium ethoxide (from 1·1 g. of sodium). After 1 hour the solution was poured into water, and the solid collected, dried on a tile and crystallised from light petroleum (b. p. 60—80°), giving 4-chloro-6-ethoxy-2-methyl-5-nitropyrimidine (9 g.), m. p. 81° (Found: C, 38·5; H, 3·5; N, 19·3. $C_7H_8O_3N_3Cl$ requires C, 38·6; H, 3·7; N, 19·2%). Similarly there were obtained *4-chloro-6-ethoxy-5-nitropyrimidine*, b. p. 134—136°/16 mm., m. p. 42° [from light petroleum (b. p. 40—60°)] (Found: C, 35·6; H, 2·9; N, 20·2. $C_6H_6O_3N_3Cl$ requires C, 35·3; H, 3·0; N, 20·6%), from 4 : 6-dichloro-5-nitropyrimidine and sodium ethoxide (1 mol.) and *4 : 6-diethoxy-2-methyl-5-nitropyrimidine*, m. p. 74° (from aqueous ethanol) (Found: C, 48·0; H, 6·1; N, 18·1. $C_9H_{13}O_4N_3$ requires C, 47·6; H, 5·7; N, 18·5%), from 4 : 6-dichloro-2-methyl-5-nitropyrimidine and sodium ethoxide (2 mols.).

Methyl 6-Ethoxy-2-methyl-5-nitro-4-pyrimidylaminoacetate.—Glycine methyl ester (4·2 g.) was added to a cold solution of 4-chloro-6-ethoxy-2-methyl-5-nitropyrimidine (5 g.) in methanol (30 c.c.). After 1 hour, the mixture was poured into water, and the solid collected and crystallised from aqueous methanol, giving *methyl 6-ethoxy-2-methyl-5-nitro-4-pyrimidylaminoacetate* (4 g.), m. p. 81° (Found: C, 44·5; H, 5·2; N, 20·2. $C_{10}H_{14}O_5N_4$ requires C, 44·4; H, 5·2; N, 20·7%).

2(6)-*Chloro-5-nitro-4-pyrimidylamino-ketones* (*Method* I).—The preparation of *2-chloro-5-nitro-4-pyrimidylaminoacetone* is typical. To a stirred solution of 2 : 4-dichloro-5-nitropyrimidine (5 g., 0·026 mol.) in dry acetone (50 c.c.), sodium hydrogen carbonate (6 g.) was added, followed by aminoacetone hydrochloride (3·5 g., 0·032 mol.) during 2 hours. The reaction mixture was then filtered, the filtrate concentrated to dryness under reduced pressure, and the residue crystallised from light petroleum (b. p. 60—80°) containing a little ethyl acetate, giving 2-chloro-5-nitro-4-pyrimidylaminoacetone.

For reactions with a 4 : 6-dichloro-5-nitropyrimidine it was advantageous to have some anhydrous magnesium sulphate present during the condensation. In the case of α-(*6-chloro-5-nitro-4-pyrimidylamino*)*deoxybenzoin* the residue left after removal of the acetone was a glass consisting predominantly of a mixture of the desired product and *5-nitro-4 : 6-di-(α-phenylphenacylamino)pyrimidine* which were separated by fractional crystallisation from light petroleum. For these and other products see Table I.

2(6)-*Amino*(*or Substituted Amino*)-*5-nitro-4-pyrimidylamino-ketones* (Method II).—The preparation of α-(*6-diethylamino-5-nitro-4-pyrimidylamino*)*deoxybenzoin* is typical. Diethylamine (7 g.), added to a solution of α-(6-chloro-5-nitro-4-pyrimidylamino)deoxybenzoin (16 g.) in ethyl acetate, produced an immediate yellow precipitate. After 4 hours the reaction mixture was evaporated to dryness and lixiviated with water to remove diethylamine hydrochloride. Crystallisation of the residue (1·65 g.) gave the desired product (1·5 g.). For this and other products see Table I.

7 : 8-*Dihydropteridines* (*Method* III).—The preparation of *4-diethylamino-7 : 8-dihydro-6 : 7-diphenylpteridine* is typical. α-(6-Diethylamino-5-nitro-4-pyrimidylamino)deoxybenzoin (2·0 g.) in methanol (25 c.c.) was hydrogenated at room temperature and pressure over Raney nickel. After filtration the solution was evaporated to dryness and the residue crystallised, giving the dihydro-compound (1·2 g.). For this and other products see Table II.

4-Diethylamino-7 : 8-dihydro-6-methylpteridine.—To 6-chloro-5-nitro-4-pyrimidylaminoacetone (2·25 g.) in ethyl acetate (25 c.c.), diethylamine (1·8 g.) was added with cooling. After 14 hours the diethylamine hydrochloride was removed and the filtrate evaporated under reduced pressure. The residual oil (2·6 g.) was reduced in methanol (30 c.c.) with hydrogen over Raney nickel at room temperature and pressure. After removal of the catalyst and solvent the residue was crystallised (see Table II).

4-Diethylamino-7 : 8-dihydro-6 : 7-dimethylpteridine.—To a stirred solution of 4 : 6-dichloro-5-nitropyrimidine (6·0 g.) in dry acetone (60 c.c.) sodium hydrogen carbonate (7·7 g.) and anhydrous sodium sulphate (6·2 g.) were added, followed, during 45 minutes, by 3-aminobutan-2-one hydrochloride (3·8 g.). After 3 hours' stirring, the inorganic salts were filtered off and the solvent evaporated under reduced pressure. The residual oil was dissolved in cold ethyl acetate and filtered and the ethyl acetate removed under reduced pressure, giving an oil (8·1 g.) which could not be induced to crystallise. This was redissolved in ethyl acetate (50 c.c.), and diethylamine (7 g.) added to the solution with cooling. After being kept overnight the diethylamine hydrochloride was filtered off and the filtrate concentrated under reduced pressure to give an oil (8·4 g.), which could not be induced to crystallise either directly or after chromatography on an alumina column. The oil (6·8 g.) was reduced in methanol (100 c.c.) at 40 lbs./sq. in. hydrogen pressure over Raney nickel. After removal of the catalyst and solvent the residue, crystallised from light petroleum (b. p. 60—80°), gave crystals (2·35 g.), m. p. 85—105°. Recrystallisation from *n*-hexane gave material (1·8 g.) of m. p. 96—99°. This was then dissolved in water (90 c.c.), and sufficient hydrochloric acid added to make the solution just acid to Congo-red. The solution was then stirred with charcoal and filtered, the filtrate basified with aqueous ammonia, and the solid collected, washed with water, dried (m. p. 106—108°), and crystallised from much water (see Table II).

Pteridines (*Method* IV).—The preparation of *4-diethylamino-6 : 7-diphenylpteridine* is typical.

(a) *By oxidation of the dihydropteridine.* To a solution of 4-diethylamino-7 : 8-dihydro-6 : 7-diphenylpteridine (0·4 g.) in acetone (25 c.c.) was added slowly, with stirring, a solution of potassium permanganate (0·12 g.) in acetone (75 c.c.). After being kept overnight and filtered, the solution was evaporated to dryness, and the residue dissolved in benzene and passed through activated alumina (15 g.). Development of the column with benzene gave an upper (unchanged material; 0·1 g.) and a lower zone which yielded 4-diethylamino-6 : 7-diphenylpteridine (0·2 g.), m. p. 156° alone or mixed with a sample prepared by method (b).

TABLE I.

α-(5-*Nitro*-4-*pyrimidylamino*)-*ketones* (II).

A.	B.	R.	R′.	Method of prepn.*	M. p.	Yield, %.	Solvent.†	Formula.	Found, %. C.	H.	N.	Cl.	Required, %. C.	H.	N.	Cl.
H	Cl	H	Me	I	60—61°	—	Pet., 2	$C_7H_7O_3N_4Cl$	Not analysed owing to rapid decomp. in air.							
Me	Cl	H	Me	I	84	—	Et_2O	$C_8H_9O_3N_4Cl$	"	"	"	"	"	"	"	"
Cl	H	H	Me	I	131	75	Pet., 1	$C_7H_7O_3N_4Cl$	36·6	3·0	24·6	—	36·4	3·0	24·3	—
Cl	Me	H	Me	I	108	68	EtOAc–Pet., 1	$C_8H_9O_3N_4Cl$	39·6	3·4	22·4	14·8	39·3	3·7	22·9	14·5
Cl	H	Me	Me	I	103	68	"	$C_8H_9O_3N_4Cl$	39·1	3·8	23·4	14·7	39·3	3·7	22·9	14·5
Cl	H	H	Ph	I	173	60	"	$C_{13}H_9O_3N_4Cl$	49·2	3·3	19·5	12·4	49·2	3·1	19·1	12·1
H	Cl	Ph	Ph	I	143	16	*n*-C_6H_{14}	$C_{18}H_{13}O_3N_4Cl$	58·5	3·5	15·0	9·8	58·6	3·5	15·2	9·6
Cl	H	Ph	Ph	I	156	45	EtOAc–Pet., 2	$C_{18}H_{13}O_3N_4Cl$	58·6	3·6	15·3	9·6	58·6	3·5	15·2	9·6
H	NEt_2	H	Me	II	—	—	—	Oil, but reduced directly								
H	$N<[CH_2]_4>O$	H	Me	II	144	61	MeOH	$C_{11}H_{13}O_4N_5$	47·0	5·5	24·6	—	47·0	5·3	24·9	—
NH_2	H	H	Me	II	216	77	Dioxan	$C_7H_9O_3N_5$	40·2	4·4	33·2	—	40·0	4·2	33·2	—
$CH_2Ph·NH$	H	H	Me	II	162	88	EtOH	$C_{14}H_{15}O_3N_5$	55·7	4·9	22·9	—	55·8	5·0	23·3	—
Et_2N	H	H	Me	II	119	98	EtOAc–Pet., 2	$C_{11}H_{17}O_3N_5$	49·1	6·3	26·5	—	49·4	6·4	26·2	—
Me	OH	H	Me	(1)	238	—	$H·CO·NMe_2$	$C_8H_{10}O_4N_4$	42·5	4·1	24·4	—	42·5	4·4	24·7	—
Et_2N	Me	H	Me	II	118	77	EtOAc–Pet., 2	$C_{12}H_{19}O_3N_5$	51·5	6·6	24·5	—	51·2	6·8	24·9	—
$CH_2Ph·NH$	H	H	Ph	II	189	94	Dioxan	$C_{19}H_{17}O_3N_5$	62·5	4·9	19·0	—	62·9	4·7	19·3	—
H	NH_2	Ph	Ph	(2)	194	—	"	$C_{18}H_{15}O_3N_5$	61·4	4·4	20·4	—	61·9	4·3	20·1	—
H	NEt_2	Ph	Ph	II	177	86	EtOAc	$C_{22}H_{23}O_3N_5$	64·8	5·7	17·3	—	65·2	5·7	17·3	—
NH_2	H	Ph	Ph	II	219 ‡	62	EtOH	$C_{18}H_{15}O_3N_5$	61·9	4·2	20·0	—	61·9	4·3	20·1	—
Et_2N	H	Ph	Ph	II	180	84	EtOAc	$C_{22}H_{23}O_3N_5$	65·4	5·6	17·2	—	65·2	5·7	17·3	—
H	CHPhBz·NH	Ph	Ph	(3)	194	—	Pet., 3	$C_{33}H_{33}O_4N_5$	70·7	4·6	12·9	—	70·7	4·6	13·0	—

* (1) Hydrolysis of the 6-chloro-compound in moist air. (2) Method II, without isolation of the 6-chloro-compound. (3) By-product from the 6-chloro-compound.

† Pet. = light petroleum: 1, b. p. 40—60°; 2, b. p. 60—80°; 3, b. p. 80—100°. ‡ With decomp.

TABLE II.

7 : 8-*Dihydropteridines* (III).

A.	B.	R.	R′.	M. p.	Yield, %.	Solvent.†	Formula.	Found, %. C.	H.	N.	Required, %. C.	H.	N.	Absorption in 0·1N-HCl, λ (mμ.) (ε in parentheses). Max.	Min.
H	NEt_2	H	Me	125°	*a*	MeOH	$C_{11}H_{17}N_5$	60·0	7·6	32·0	60·2	7·8	32·0	230 (14,400), 343 (12,000)	280 (1,800)
H	NEt_2	Me	Me	109	—	H_2O	$C_{12}H_{19}N_5$	62·1	7·7	29·7	61·8	8·1	30·0	—	—
H	$N<[CH_2]_4>O$	H	Me	152	72	C_6H_6	$C_{11}H_{15}ON_5$	56·7	6·3	30·0	56·7	6·4	30·0	247 (15,000), 305 (12,300)	280 (5,300)
H	NH_2	Ph	Ph	266	79	EtOH	$C_{16}H_{13}N_5$	71·4	4·9	22·8	71·8	5·0	23·2	257 (25,400), 370 (9,300)	315 (1,700),
H	NEt_2	Ph	Ph	168	67	EtOAc–Pet., 3	$C_{22}H_{23}N_5$	73·3	6·4	19·4	73·9	6·4	19·6	230 (23,800), 265 (21,300), 310 (13,100), 385 (11,000)	250 (18,000), 290 (10,500), 334 (3,500)
NH_2	H	H	Me	240 *	65	H_2O	$C_7H_9N_5$	51·3	5·4	43·2	51·5	5·6	42·0	290 (7,400)	260 (3,700)
Et_2N	H	H	Me	158	70	MeOH	$C_{11}H_{17}N_5$	60·0	7·6	32·0	60·3	7·8	32·0	250 (8,500)	—
$CH_2Ph·NH$	H	H	Ph	242	70	EtOH–dioxan	$C_{19}H_{17}N_5$	72·8	5·0	22·1	72·4	5·4	22·2	—	—
NH_2	H	Ph	Ph	246	71	EtOH	$C_{16}H_{13}N_5$	71·6	5·0	23·0	71·8	5·0	23·3	232 (24,700), 335 (13,800)	305 (8,400)
Et_2N	H	Ph	Ph	139	81	MeOH–H_2O	$C_{22}H_{23}N_5$	73·5	6·4	19·8	73·9	6·4	19·6	232 (27,800), 280 (13,300), 337 (15,300)	265 (11,300), 312 (8,400)
Et_2N	Me	H	Me	121	70	Pet., 2	$C_{13}H_{19}N_5$	61·9	8·1	29·7	61·8	8·2	30·0	—	—

* With decomp. * 65% from crude amino-ketone. † Pet., see Table I, footnote.

TABLE III.

Pteridines (substituents as in III).

A.	B.	R.	R'.	Method of prepn.	M. p.	Yield, %.	Solvent.	Formula.	Found, %. C.	H.	N.	Required, %. C.	H	N.	Absorption in 0·1N-HCl, λ (mμ.) (ε in parentheses). Max.	Min.
NH_2	H	H	Me	IVa	>250° *	50	H_2O	$C_7H_7N_5$	51·9	4·4	44·0	52·2	4·3	43·5	235 (9,300), 305 (6,400)	265 (1,800)
NH_2	H	Ph	Ph	IVa	244	94	EtOH	$C_{18}H_{15}N_5$	72·6	4·2	23·0	72·2	4·3	23·4	275 (12,900), 335 (14,800)	255 (10,500), 320 (6,600)
				IVb												
Et_2N	H	Ph	Ph	IVa	147	57	Pet., 2	$C_{22}H_{21}N_5$	74·2	6·2	19·9	74·4	5·9	19·7	230 (29,300), 273 (14,600), 335 (14,800)	260 (12,900), 305 (8,600)
H	NH_2	Ph	Ph	IVa	210	90	MeOH–EtOAc	$C_{18}H_{15}N_5$	72·0	4·5	23·4	72·2	4·3	23·4	278 (12,800), 375 (15,100)	265 (10,700), 325 (6,100)
				IVb		5										
H	NEt_2	H	H	IVb	112	40	Pet., 2	$C_{10}H_{13}N_5$	59·1	6·2	34·0	59·1	6·4	34·5	228 (14,100),	280 (8,900)
Picrate					169		H_2O	$C_{16}H_{16}O_7N_8$	44·0	3·9	25·5	44·4	3·7	25·9	340 (12,800)	
H	NEt_2	Me	Me	IVa	85	75	*n*-C_6H_{14}	$C_{12}H_{17}N_5$	62·0	7·3	30·5	62·3	7·4	30·3	235 (15,500), 340 (14,800)	280 (1,700)
				IVb		50										
H	NEt_2	Ph	Ph	IVa	158	66	MeOH–H_2O	$C_{22}H_{21}N_5$	74·0	6·0	20·2	74·4	5·9	19·7	395 (22,700)	270 (9,000)
				IVb		52										
H	NEt_2	*p*-C_6H_4Cl	*p*-C_6H_4Cl	IVb	162	9	EtOH	$C_{22}H_{19}N_5Cl_2$	62·3	4·5	16·2†	62·2	4·5	16·5	—	—
H	NEt_2	7 : 8-Acenaphthylenylene		IVb	248	75	C_6H_6	$C_{20}H_{17}N_5$	73·4	5·0	21·0	73·4	5·2	21·4	282 (14,600), 340 (29,000)	260 (11,200), 300 (11,500)
H	NEt_2	9 : 10-Phenanthrylene		IVb	185	89	C_6H_6	$C_{22}H_{19}N_5$	74·9	5·4	19·9	74·8	5·4	19·8	235 (42,700), 305 (11,400) 412 (13,500)	285 (9,700), 345 (2,900)
H	NEt_2	2-Furyl	2-Furyl	IVb	164	50	MeOH	$C_{18}H_{17}O_2N_5$	64·1	4·8	20·9	64·5	5·1	20·9	—	—

* With decomp. † Found: Cl, 16·0. Reqd.: Cl, 16·7%.

(b) *Condensation of a* 4 : 5-*diaminopyrimidine with an* α-*diketone.* 5 : 6-Diamino-4-diethylaminopyrimidine (3·5 g.), benzil (4·5 g.), and ethanol (100 c.c.) were heated under reflux for 24 hours. After removal of the ethanol the residue was dissolved in dilute hydrochloric acid, and the solution extracted with light petroleum and basified with aqueous sodium hydroxide. The precipitated solid was collected and crystallised from aqueous methanol, giving 4-diethylamino-6 : 7-diphenylpteridine (3·6 g.), m. p. 157—158° (Found : C, 74·0; H, 6·0; N, 20·2. $C_{22}H_{21}N_5$ requires C, 74·4; H, 5·9; N, 19·7%).

For other pteridines prepared see Table III.

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HEXAGON HOUSE, BLACKLEY, MANCHESTER, 9. [*Received, November* 14*th*, 1950.]

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127. *The Enzymic Synthesis and Degradation of Starch. Part XII. The Mechanism of Synthesis of Amylopectin.*

By P. N. HOBSON, W. J. WHELAN, and S. PEAT.

Evidence is presented which necessitates a modification of the hypothesis proposed earlier (*J.*, 1945, 877) whereby the synthesis of amylopectin from glucose-1 phosphate was pictured as involving the intermediate formation of short unbranched chains of glucose units (pseudoamylose). It is now shown that the synthesis proceeds as follows :

$$\text{Glucose-1 phosphate} \underset{\text{Phosphorylase}}{\rightleftharpoons} \text{Amylose} \xrightarrow{\text{Q-enzyme}} \text{Amylopectin}$$

THE synthesis of starch from glucose-1 phosphate is brought about by at least two enzymes, phosphorylase and Q-enzyme. The former when acting alone synthesises the amylose component of starch, whilst the combined action of both enzymes leads to the synthesis of the ramified component, amylopectin. In addition Q-enzyme, acting in the absence of other enzymes or of phosphates, has the property of converting amylose into amylopectin (see Barker, Bourne, Wilkinson, and Peat, *J.*, 1950, 93, and earlier papers of this series). The interrelationships of these polysaccharides and enzymes were discussed by Bourne and Peat in 1945 (*J.*, p. 877) when it was suggested, as a working hypothesis, that the synthesis of amylopectin involved the formation of an intermediate polysaccharide (pseudoamylose) consisting of unbranched chains averaging *ca.* 20 glucose units in length and therefore equivalent to the basal chains of amylopectin. In the synthesis of amylopectin from glucose-1 phosphate, Q-enzyme was thought to establish 1 : 6-links between the short chains of " pseudoamylose," the latter being synthesised by the phosphorylase. For the conversion of amylose into amylopectin, the hypothesis requires Q-enzyme to possess a second function, namely, the fragmentation of amylose (by scission of 1 : 4-links) with the formation of the short chains of " pseudoamylose."

This hypothesis does not, however, cover all the facts of starch synthesis. In the first place, it assumes that both functions of Q-enzyme are operative in the conversion of amylose into amylopectin but that only one, the branching function, operates in the synthesis of amylopectin from the Cori ester. Again, in the case where the pseudoamylose chains are formed from glucose-1 phosphate by phosphorylase, it is difficult to see what could be the source of the energy required for the mutual combination of these chains by Q-enzyme. Evidence is now presented which favours a modified form of the original, admittedly tentative, hypothesis.

A series of dextrins were prepared *in situ* by fragmentation of the chains of potato amylose by salivary α-amylase. The digests were boiled to destroy the α-amylase and then treated with potato Q-enzyme. After incubation at 21° (for the same time as was necessary for the formation of amylopectin from the original amylose) the Q-enzyme was inactivated by heat, and the limits of conversion of the residual polysaccharides into maltose by soya-bean β-amylase were determined at pH 4·8. These values were compared with the β-amylolysis limits of the same α-dextrins before treatment with Q-enzyme. The difference in these conversion limits before and after Q-enzyme action is a measure of the extent to which the particular α-dextrin can serve as substrate for the branching action of Q-enzyme. At the same time the blue values of the α-dextrins were estimated.

The results, summarised in the Table, show that the ability of Q-enzyme to utilise the α-dextrins in the synthesis of branched polysaccharides diminishes as the blue value, and

therefore as the average chain-length, decreases. Dextrins with blue values of less than 0·45 are incapable of acting as substrates for the synthetic action of Q-enzyme, the β-amylolysis limits indicating that no additional branching is introduced into these dextrins by Q-enzyme.

α-Dextrins as substrates for Q-enzyme.

Blue value of the α-dextrin.	Limiting conversion by β-amylase (%): before Q-action.	after Q-action.	difference.	Blue value of the α-dextrin.	Limiting conversion by β-amylase (%): before Q-action.	after Q-action.	difference.
1·20 *	85·0	55·0	30·0	0·449	83·1	81·7	1·4
1·01	84·2	62·7	21·5	0·340	86·2	87·4	−1·2
0·847	82·2	69·7	12·5	0·137	86·8	86·8	0·0
0·544	84·4	79·9	4·5				

* Untreated amylose.

Measurement of the reducing power of the dextrins of blue value 0·45 suggests that the average chain-length is not less than 25 glucose units and is probably much greater.

The inference from these results is that Q-enzyme cannot link together the chains of " pseudoamylose." This supposition has been confirmed by making use of the " debranching " R-enzyme recently discovered in the broad bean and potato by Hobson, Whelan, and Peat (*Biochem. J.*, 1950, **47**, xxxix). R-Enzyme hydrolyses the branch-linkages of amylopectin, and the product is therefore akin to " pseudoamylose." Q-Enzyme is without action on this product, as is indicated by the negligible change in degree of β-amylolysis after Q-enzyme action. It therefore appears that the synthesis of a 1 : 6-link by Q-enzyme must be preceded by the scission of a 1 : 4-link, in which case the action of Q-enzyme is that of a transglycosidase and the energy needed for the synthesis of the 1 : 6-link is provided by that liberated in the scission of the 1 : 4-link. Furthermore, it is clear that scission and synthesis are interdependent and probably occur simultaneously.

Experiments are now in progress to determine the minimum length of chain which will serve as a substrate for Q-enzyme action. There are indications that this chain-length is not far short of that of natural amylose. In this case the path of synthesis of amylopectin from glucose-1 phosphate would be :

$$\text{Glucose-1 phosphate} \xrightleftharpoons{\text{Phosphorylase}} \text{Amylose} \xrightarrow{\text{Q-enzyme}} \text{Amylopectin}$$

We are satisfied that the action of Q-enzyme is irreversible in a practical sense and that no conversion of amylopectin into amylose occurs by its agency (see Part VII, *J.*, 1950, 93). The question therefore arises as to why amylose is found in any plant in which a " branching " enzyme is present. It may be that the physical environment of synthesis is such that part of the amylose formed from the Cori ester is not susceptible to attack by Q-enzyme.

Experimental.

Analytical Methods.—For the methods used in measurement of the iodine stains of polysaccharides and in determination of reducing sugar and β-amylase activity see Part X (*J.*, 1950, 3566).

Preparation of Enzymes.—(*a*) Salivary α-amylase was prepared by diluting saliva one hundred times and centrifuging.

(*b*) Soya-bean β-amylase was prepared as in Part II (*J.*, 1945, 882). It was dissolved in 0·2M-acetate buffer, pH 4·8, to give an activity of 440 units/c.c., the insoluble residue being removed on a centrifuge.

(*c*) Potato Q-enzyme (Q3-fraction) was isolated as a freeze-dried powder by the method given in Part IV (*J.*, 1949, 1705).

(*d*) R-Enzyme was isolated as an acetone-dried powder from broad bean (Suttons' " Prolific Longpod ") by the method given in Part XIV (*J.*, to be published).

Fractionation of Potato Starch.—Amylose and amylopectin were separated by the thymol method of Bourne, Donnison, Haworth, and Peat (*J.*, 1948, 1687). The amylopectin was further fractionated by using the procedure of Part XIII (*J.*, to be published). An amylose of high blue value, prepared as in Part XIII, could not be used in the following experiments because of the partial precipitation of the polysaccharide which occurs on the addition of either Q-enzyme or α-amylase.

Successive Actions of α-Amylase, Q-Enzyme, and β-Amylase on Amylose.—Amylose (B.V., 1·20; 52·0 mg.), contained in a 50-c.c. standard flask, was dissolved in 0·1N-sodium hydroxide solution (20 c.c.) by warming the mixture gently with shaking. The solution was neutralised with 0·2N-H_2SO_4, 0·2M-acetate buffer (pH 7·0; 5 c.c.) and salivary α-amylase (3 c.c.) were added, and the solution was diluted

to 50 c.c. The digest was kept at 21° and at intervals portions were removed for determination of blue value. At chosen times two portions (10 c.c. each) were transferred to dry 25-c.c. standard flasks and heated for 10 minutes in a boiling water-bath. After cooling, 0·2M-acetate buffer (pH 7·0; 2 c.c. each) was added to the digests and to one was added water (3 c.c.), to the other Q-enzyme solution (3 c.c.; 67 mg.). After incubation at 21° for 2 hours the enzyme was heat-inactivated as above, and after being cooled, N-acetic acid (0·35 c.c., to adjust the pH to 4·8), β-amylase solution (2 c.c.), and water (to 25 c.c.) were added. The digests were incubated at 35·5° and the reducing powers, as maltose, were determined at intervals; the values became constant after 6 hours. Corresponding blank digests containing enzymes and buffer but without the polysaccharide were incubated at the same time in order to determine the reducing powers of the enzymes. Each digest with α-amylase provided two samples of α-dextrin. Three determinations were made by the procedure described above and hence the values for six α-dextrins are recorded in the Table. The results for the original amylose were obtained by the same procedure except that no α-amylase was used.

Successive Actions of R-Enzyme, Q-Enzyme, and β-Amylase on Amylopectin.—Digests were prepared, all of which contained amylopectin (10 c.c.; 18·7 mg.), 0·2M-acetate buffer (pH 7·0; 3 c.c.), and water (3·7 c.c.). In addition digest (1) contained water (2 c.c.), and digests (2) and (3) R-enzyme solution (2 c.c., 56 mg.). The digests were incubated at 21° for 21 hours, then portions (0·5 c.c.) were removed for determination of blue value, and the enzyme was destroyed by heat. To each, after it had been cooled, was added 0·2M-acetate buffer (pH 7·0; 1 c.c.); in addition, to digest (2) was added Q-enzyme solution (2 c.c.; 49 mg.), and to each water to 25 c.c. These digests were incubated at 21° for 6 hours and, after removal of portions (0·69 c.c.) for determinations of blue value, the digests were heated in boiling water for 10 minutes. The β-amylolysis limits of portions (20 c.c. each) were determined by the addition of acetic acid and β-amylase as described above.

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UNIVERSITY COLLEGE OF NORTH WALES, BANGOR. [*Received, November 27th*, 1950.]

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128. *The Kinetics of the Dissolution of Zinc in Aqueous Iodine Solutions. Part I.*

By L. L. BIRCUMSHAW and A. C. RIDDIFORD.

A preliminary study of the rate of dissolution of zinc in aqueous iodine solutions has been made. The observed rate is of first order with respect to the iodine concentration and is directly proportional to the apparent surface area of the zinc specimen over the range investigated. With the exception of specimens polished with rouge, the method of preparation of the surface is without effect on the rate. The rate is independent of the initial concentration of acid over the range N/100 to N/800. Over the temperature range 25—45°, the experimental energy of activation is 3790 cals. per mole. The energy of activation for kinematic viscous flow over the same range is 3570 cals. per mole.

COMPARATIVELY little work has been reported on the kinetics of reactions between metals and solutions of halogens. Schükarew (*Z. physikal. Chem.*, 1891, **8**, 76) investigated the rate of reaction between certain metals and iodine, but failure to provide for constant and effective stirring renders his results of uncertain value. Brunner (*ibid.*, 1905, **51**, 95) performed a few experiments on the dissolution of zinc in aqueous iodine solutions and concluded that iodine is reduced by zinc at the same rate as it is reduced electrolytically at a platinum electrode.

The major part of the work in this field has been done by Van Name and his co-workers (Van Name and Edgar, *Amer. J. Sci.*, 1910, **29**, 237; Van Name and Bosworth, *ibid.*, 1911, **32**, 207; Van Name and Hill, *ibid.*, 1913, **36**, 543; Van Name, *ibid.*, 1917, **43**, 449). Their results may be summarised as follows: (1) Under the same conditions, mercury, cadmium, zinc, copper, silver, iron, nickel, and cobalt dissolve in aqueous iodine solutions containing a large excess of potassium iodide at practically the same rate. A slight decrease in the rate of dissolution of copper and silver was attributed to the presence of traces of solid iodide at the interface. (2) The rate constants for tin and magnesium were found to be higher. For tin, the increase

was ascribed to the two-stage oxidation of tin to the stannic state; for magnesium, it was thought to be due to increased stirring of the solution by the hydrogen evolved. (3) An increase in the concentration of potassium iodide produces a marked acceleration of the rate. (4) The rate is approximately proportional to the 0·8 power of the rate of stirring. (5) The observed rate decreases with increase in the viscosity of the solution and is consistently lower than the corresponding value calculated from the Arrhenius diffusion equation (*Z. physikal. Chem.*, **1892**, **10**, 51). (6) The mean temperature coefficient of the reaction is 1·26 per 10° over the range 0—65°. Moelwyn-Hughes (" Kinetics of Reactions in Solution," 2nd edn., 1947, p. 357) has calculated the energy of activation to be 4040 cals. per mole.

These observations are consistent with the view that the rate is determined by the rate of transport of iodine to the metal surface. Van Name and Edgar ascribed the increase of rate with increasing potassium iodide concentration to an increase in the diffusion coefficient of the tri-iodide ion. Edgar and Diggs (*J. Amer. Chem. Soc.*, 1916, **38**, 253) confirmed this view by measuring the diffusion coefficient at 25°. They were unable, however, to correlate the change in diffusion coefficient with the change in viscosity of the solution. Similar results have been obtained by Miller (*Proc. Roy. Soc.*, 1924, *A*, **106**, 724).

Bircumshaw and Everdell (*J.*, 1942, 598) made a further study of the reaction between copper and aqueous iodine solutions, and found that for a large range of iodine concentrations the rate of reaction is unaffected by the presence or thickness of cuprous iodide films, and postulated that the reaction proceeds by the passage of both iodine and solvent through the iodide film. The rate of reaction is not dependent on the method of preparation, or degree of smoothness of the metal surface, and is unaffected by the rate of stirring provided that this is fairly high. The rate increases with increasing concentration of potassium iodide, as found by Van Name and Edgar. Bircumshaw and Everdell (*J.*, 1947, 1119) also investigated the rate of reaction between copper and solutions of iodine in organic solvents. Here the rate of reaction appears to be partly controlled by the thickness of the iodide film. The resistance to mass transfer of an iodide film has also been reported by Evans and Bannister (*Proc. Roy. Soc.*, 1929, *A*, **125**, 370). Trotman-Dickenson and James (*J.*, 1947, 736) have studied the reaction between tin and solutions of bromine and iodine in organic solvents, their results being in accord with the simple Nernst theory.

In recent years attention has been directed towards replacement of Nernst's diffusion theory by a more adequate theoretical treatment. The complex geometry of most experimental systems precludes the complete calculation of mass transfer by convection in terms of the fluid flow in the system. By analogy with the closely related study of heat transfer, however, a semi-quantitative treatment using dimensional analysis has been developed (for details and references see Agar, *Faraday Soc. Discussion*, 1947, **1**, 26). In view of the ease with which the reaction may be followed, and the absence of complicating factors such as the formation of an insoluble film on the metal surface, gas evolution, etc., the dissolution of certain metals in aqueous iodine solutions is very suitable for the study of mass transfer in solid–liquid systems. It seemed desirable, therefore, to make a more detailed study of the kinetics of the dissolution of zinc in aqueous iodine solutions with the object of confirming that the rate is determined solely by the rate of transport of iodine to the surface.

This paper reports the investigation of the following factors: (1) The surface area of the zinc specimen; (2) the method of preparing the metal surface; (3) the temperature; (4) the initial concentration of iodine; (5) the initial concentration of acid.

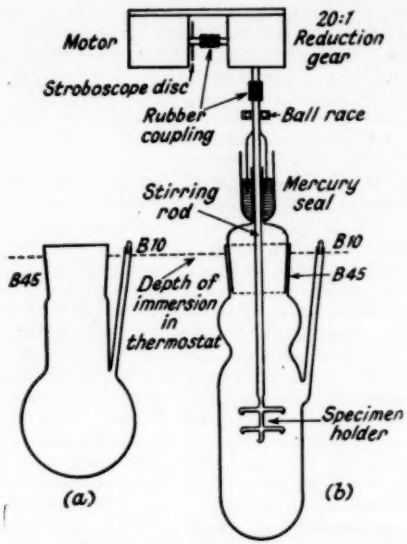
Experimental.

Materials.—" AnalaR " iodine, potassium iodide, and sodium thiosulphate were used without further purification. The absolute alcohol and benzene used in the preparation of the metal specimens were dried and redistilled before use. The zinc foil, reported to contain Fe 0·005%, Cu 0·002%, and traces of cadmium and lead, was kindly supplied by London Zinc Mills, Ltd.

Apparatus.—The apparatus was an improved form of the type used by Bircumshaw and Everdell (*loc. cit.*, 1947), and is shown in Fig. 1(*b*). The reaction vessel, mercury seal, and stirring rod are drawn to approximately one-fifth scale. The glass specimen holder was constructed so that the edges of the specimen only touched the glass at five points. The holder was slightly off-set so that the axis of the stirrer was in line with the vertical axis of the specimen. The stirrer was driven through a 20 : 1 helical reduction gear by means of a 0·02 H.P. motor. To ensure constant rates of stirring, the motor was controlled by means of a constant-voltage transformer and " Variac " transformer, a stroboscope being used. Tests showed that with this arrangement the rate of stirring could be maintained constant by manual control to within 1%. The glass sleeve of the seal was lubricated lightly with glycerol. This sleeve, together with the ball-race, ensured the absence of " whip " at the lower end of the stirring rod. The motor, stirrer, and mercury seal were mounted in fixed positions on a carrier so that the whole assembly could be raised vertically until the stirrer was out of the reaction vessel. This arrangement ensured that the geometry of the system was the same for all experiments. Fig. 1(*a*) shows a second

reaction vessel used in certain experiments described in Part III of this work. It is shown here in order to facilitate comparison with the standard reaction vessel. The thermostat maintained the temperature constant to within ± 0·01°. The burette, pipettes, and thermometers used were calibrated.

FIG. 1.



Standard Preparation of the Zinc Specimen.—The standard specimen size was 4·0 × 3·0 cm., cut from foil 0·039 cm. thick. The dimensions of each specimen were determined by means of Vernier calipers and micrometer before use. Corrections were applied for the slight variations from the standard dimensions. The standard method of preparing the surface was to clean the specimen with cotton-wool soaked in a commercial metal-polish. The specimen was polished with clean cotton-wool until all the metal-polish had been removed. It was next washed thoroughly with distilled water, twice in absolute alcohol, and finally in pure, dry benzene. It was then dried in air and used immediately.

Method.—Unless otherwise stated, the iodine solutions contained 4 mols. of potassium iodide per atom of iodine. The standard initial iodine concentration was N/25. As found by Van Name and Edgar (*loc. cit.*), the velocity constant, in the absence of acid, falls off with time owing to the deposition of zinc hydroxide on the metal surface. To prevent this, the iodine solutions were made 0·01N. with respect to sulphuric acid immediately before use.

The standard procedure was as follows: 300 Ml. of the acidified iodine solution were transferred to the reaction vessel. The stirrer assembly and specimen were lowered into the reaction vessel, the stirrer motor was started, and the rate of stirring adjusted to the required speed by observation of the stroboscope. The standard rate of stirring was 100 r.p.m. Preliminary tests showed that two or three minutes were necessary before the rate of stirring became constant. Zero time was therefore taken as the time of withdrawal of the first sample. 5-Ml. samples were withdrawn at 5-min. intervals, and titrated with standard sodium thiosulphate. In this manner, all samples were withdrawn under exactly similar conditions. The time required for withdrawing a 5-ml. sample was approximately 5 secs., so that no appreciable loss of iodine took place. Blank runs, in which the specimen was replaced by a piece of glass cut to the same dimensions, confirmed that the loss of iodine by evaporation at 25° and 45° was negligible. With few exceptions, experiments were performed at least in duplicate. Standard runs were conducted at frequent intervals to ensure the constancy of the apparatus.

Surface Area of the Zinc Specimen.—Three sizes were studied, the standard size, 3·0 × 3·5 cm., and 3·0 × 3·0 cm. Table I shows the observed values of the velocity constant. The reaction is of first order

TABLE I.

Initial concentration of iodine = N/25; 100 r.p.m.; 25°.

Dimensions of specimen, cm.	3·0 × 3·0	3·0 × 3·5	3·0 × 4·0
k_1 (obs.), cm. min.$^{-1}$	0·133, 0·133	0·133, 0·130	0·133, 0·133

with respect to the iodine concentration, *i.e.*, $2{\cdot}303v.\mathrm{d}(\log c)/\mathrm{d}t = -kc$, where v is the volume of solution in ml., c is the concentration of iodine in g.-atoms per litre, and k is the velocity constant. Allowance must be made for the stepwise change in the volume of solution. The velocity constant per unit area, k_1, was evaluated graphically by means of the expression: $k_1 t = \frac{2{\cdot}303}{A} \Sigma v \,.\, \Delta \log c$, where t is the time in

minutes, A is the area in sq. cm., and $\Delta \log c$ signifies the difference in log c at the beginning and end of an interval for which the volume is v (Bradley, *Trans. Faraday Soc.*, 1938, **34**, 278).

Influence of the Method of Preparation of the Surface.—In addition to the standard method of preparing the zinc surface, eight other methods were investigated, including etching it with acid for periods between 5 and 60 secs., abrasion with carborundum powder, polishing with concentrated nitric acid, electrolytic polishing (see Lacombe, Morize, and Chaudron, *Rev. mét.*, 1947, **44**, 87), and polishing with jeweller's rouge. With the exception of the last, the method of preparation of the surface was without effect on the observed rate within the limits of experimental error (mean value of $k_1 = 0{\cdot}131$ cm. min.$^{-1}$). A marked increase in rate was observed for specimens polished with rouge ($k_1 = 0{\cdot}144$, $0{\cdot}146$ cm. min.$^{-1}$). Surfaces so prepared show a coloured appearance, with marked scratches. Under the microscope, particles of rouge are seen embedded in the metal. The plot of $(\Sigma v \,.\, \Delta \log c)/A$ against t is shown in Fig. 2, together with the graph for a run with an electrolytically polished specimen.

FIG. 2.

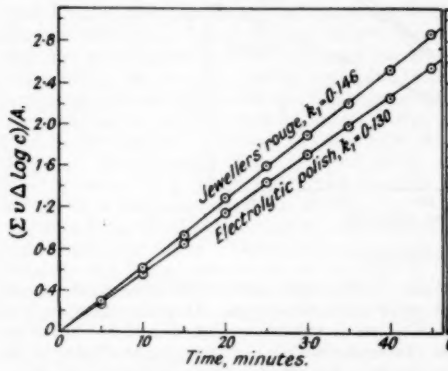
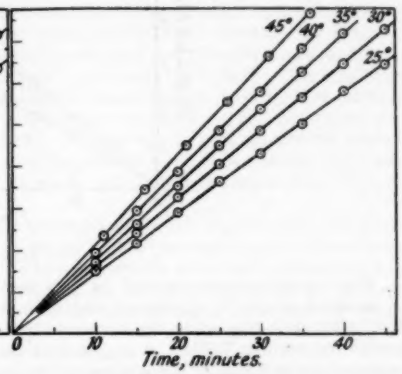


FIG. 3.



Temperature Coefficient.—The rate of reaction was studied at five temperatures over the range 25—45°. The observed values of k_1 are recorded in Table II. Fig. 3 shows the plot of $(\Sigma v \,.\, \Delta \log c)/A$ against t for one run at each temperature. In each case the initial concentration of iodine was N/25, and the rate of stirring 100 r.p.m. The kinematic viscosity, ν, and the density of the iodine solutions were determined at each temperature. The kinematic viscosity was determined with an Ostwald type viscometer corrected for deviations from Poiseuille's law. Values for the absolute kinematic viscosity of water were taken from Bingham and Jackson's results (Goldstein, "Modern Developments in Fluid Dynamics," 1943, Vol. I, p. 5), and values for the density of water from Chappuis's data (Kolthoff and Sandell, "Textbook of Quantitative Inorganic Analysis," 1946, p. 764).

TABLE II.

Temp.	k_1 (obs.), cm. min.$^{-1}$.	Mean k_1, cm. min.$^{-1}$.	d, g./ml.	ν, centistokes.
25°	0·133, 0·132, 0·133, 0·132	0·133	1·0205	0·870
30	0·150, 0·150, 0·149, 0·147, 0·148	0·149	1·0204	0·783
35	0·164, 0·168, 0·164, 0·163, 0·164, 0·165, 0·164, 0·169	0·165	1·0188	0·708
40	0·182, 0·179, 0·183	0·181	1·0180	0·648
45	0·191, 0·200, 0·208, 0·197, 0·195	0·198	1·0162	0·597

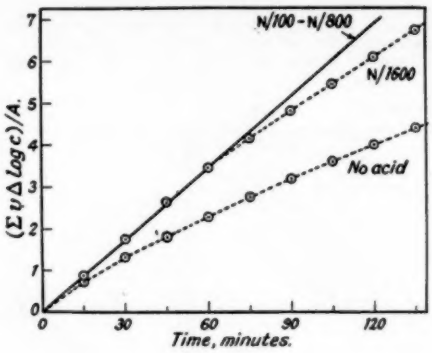
Initial Concentration of Iodine.—The effect of varying the initial concentration of iodine over the range 0·002—0·16N. was studied at 25° and 100 r.p.m. With the exception of the 0·002N-solution, which did not contain potassium iodide, the solutions always contained 4 g.-equivs. of this salt per g.-equiv. of iodine initially present. A 1% solution of sodium starch glycollate (1 : 10) (Peat, Bourne, and Thrower, *Nature*, 1947, **159**, 810) was used as indicator for the titrations. The observed values of k_1 are recorded in Table III, together with the determined values of the kinematic viscosity and density of the iodine solutions.

TABLE III.

Initial concn. of I, g.-equiv./l.	k_1 (obs.), cm. min.$^{-1}$.	Mean k_1, cm. min.$^{-1}$.	d, g./ml.	ν, centistokes.
0·002	0·129, 0·129	0·129	0·9972	0·903
0·005	0·129, 0·127	0·128	1·0009	0·897
0·01	0·129, 0·128	0·129	1·0025	0·891
0·02	0·131, 0·129	0·130	1·0087	0·883
0·04	0·131	0·131	1·0205	0·870
0·08	0·131, 0·135, 0·134	0·133	1·0404	0·846
0·16	0·136, 0·136	0·136	1·0888	0·799

Initial Concentration of Acid.—The effect of varying the initial concentration of sulphuric acid over the range 0—0·01N. was investigated. 5-Ml. samples were withdrawn every 15 mins. The results are shown in Fig. 4 (the experimental points for the runs using N/100-, N/200-, N/400-, and N/800-acid fall closely on the full line, and have been omitted for the sake of clarity). In each case, the initial concentration of iodine was N/25, the rate of stirring and temperature being standard.

FIG. 4.



DISCUSSION.

The investigations reported in this section of the work were conducted with a view to establish standard conditions and as such need little discussion. That the reaction is of first order with respect to the concentration of iodine is shown by Figs. 2 and 3. From the results reported in Table I, it is seen that the observed velocity is directly proportional to the apparent surface area of the specimen over the range investigated. It is permissible, therefore, to correct for the slight variations in size of different specimens from the standard dimensions. Such corrections, and in particular the reduction of the observed velocity constant to unit area, do not imply that the rate of reaction is uniform over the whole area of the surface. From general considerations this would seem unlikely for systems of the geometrical form used in this investigation. Under certain conditions the rate can be shown to differ at different points on the surface. Evidence in support of this view will be reported in Part III. Nevertheless, the use of the rate constant per unit area, k_1, may be justified by regarding it as the average rate per unit area. As will be seen from the results, it is reproducible.

With the exception of specimens polished with rouge, the method of preparing the surface appears to be without effect on the observed rate. The fact that scratched or deeply etched specimens react at the same rate as highly polished specimens would seem to indicate that the rate is dependent on the apparent area, and not on the true surface area. This would follow from the simple Nernst diffusion theory provided the height of the surface irregularities is small compared with the mean thickness of the diffusion layer (see Brunner and Tolloczko, *Z. physikal. Chem.*, 1900, **35**, 283). In terms of the fluid flow in the system, the picture is rather more complex. The relative roughness of the surface is defined as the ratio of the mean height of the surface irregularities to the characteristic length of the system. For fluid flow through a pipe, where the characteristic length is taken to be the internal diameter of the pipe, Nikuradse (*Forschungsheft* No. 361, Suppl. to *Forschung auf dem Gebiete des Ingenieurwesens*, 1933, 4*B*, July/August) has shown that wall roughness over the range 1/507 to 1/15 is without effect on the friction factor in the region of laminar flow, but that it has considerable effect in the case of turbulent flow. In a later part of this work it will be shown that there are grounds for believing the flow to be non-turbulent under the experimental conditions used in this investigation. One would therefore expect the method of preparing the surface to be without effect on the observed rate, provided that the rate is determined solely by the rate of a transport process. The penetration of rouge into a zinc surface when used as a polishing agent has also been reported by Vernon, Akeroyd, and Stroud (*J. Inst. Metals*, 1939, **65**, 301) in their study of the rate of oxidation of zinc. For this reaction, the rouge appeared to have little effect on the observed rate. No explanation has been found for the marked increase in rate for the reaction with iodine.

The mean temperature coefficient over the range 25—45° is 1·22 per 10°, *i.e.*, of the same order as that of the diffusion coefficients of several solutes in liquids over the same range. Applying the method of least squares to the 25 values of k_1 recorded in Table II, we find the velocity constant per unit area to be given by the expression $k_1 = 78{\cdot}1 \exp.(-3790/RT)$. E_A, the experimental energy of activation, is in good agreement with the value 4040 cals./mole calculated from Van Name's data for cadmium by Moelwyn-Hughes (*loc. cit.*). Edgar and Diggs (*loc. cit.*) studied the diffusion of iodine in potassium iodide solutions at 25°. Miller's investigations were similarly confined to one temperature (19·91°). From their results, the activation energy of the diffusion process, E_D, is about 5000 cals./mole, the small temperature range making any closer evaluation impossible.

The influence of viscosity on the rate of reaction has been studied in more detail, and will be reported in Part II. It will be shown that the observed rate is a function of the kinematic viscosity (*i.e.*, the ratio of the coefficient of dynamic viscosity to the density) rather than of the dynamic viscosity. It was for this reason that no effort was made to measure the densities with any great accuracy. The values of the kinematic viscosity are thought to be correct to within 0·5%, and are given by the expression $\nu = 2{\cdot}10 \times 10^{-5} \exp.(3570/RT)$. The similarity in magnitude between the activation energy for kinematic viscous flow, E_ν, and E_A is of interest. It is usual to find values of the activation energy for dynamic viscous flow, E_η, slightly smaller than E_D (see Taylor, *J. Chem. Physics*, 1938, **6**, 331). Similarly, E_ν will usually be smaller than E_D. Thus, Orr and Butler (*J.*, 1935, 1273), studying the diffusion of deuterium hydroxide in water, found E_D to be 5300 cals./mole over the range 0—45°. Over the same range, both E_η and E_ν have the same value, *viz.* 4200 cals./mole.

From Table III it is seen that the observed rate constant varies but slightly with the initial concentration of iodine. Variation is most marked at the higher concentrations, and is almost certainly due to the lowering of the viscosity of the solution by the increased concentration of potassium iodide. The variation is not large enough to show whether k_1 is inversely proportional to the viscosity. With the exception of the two largest values, all the values of k_1 are constant within the limits of experimental error. It is of interest to note that the velocity in the absence of potassium iodide is of the same value.

Variation of the initial concentration of acid over the range N/100—N/800 is without effect on the observed rate. The fall in the rate with time in the absence of acid is marked, and moreover is not reproducible. Examination of specimens after runs without acid shows that the surface is covered irregularly with white patches of hydroxide.

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THE UNIVERSITY, EDGBASTON, BIRMINGHAM.
UNIVERSITY COLLEGE OF NORTH WALES, BANGOR. [*Received, September 27th*, 1950.]

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129. *Organic Fluorides. Part VI. The Chemical and Physical Properties of Certain Fluorocarbons.*

By R. N. HASZELDINE and F. SMITH.

The boiling points, densities, refractive indices, and surface tensions of a number of fluorocarbons have been determined, and the variation of certain of these properties with temperature has been investigated.

IN Parts I—V of this series (*J.*, 1949, 3021, 3026; 1950, 2689, 2787, 3617) the preparation of fluorocarbons by the interaction of fluorine and of cobalt trifluoride with hydrocarbons was described. The present communication records physical properties of certain fluorocarbons the preparation of which was described in Parts III—V.

The pure fluorocarbons available were: in the *n*-perfluoroparaffin series, C_7F_{16}, C_8F_{18}, C_9F_{20}, $C_{10}F_{22}$, $C_{11}F_{24}$, $C_{12}F_{26}$, and $C_{16}F_{34}$; the following monocyclic compounds, C_7F_{14}, C_8F_{16} (from *m*-xylene), C_9F_{18} (from mesitylene), and $C_{10}F_{20}$ (from *p*-cymene); and two bicyclic com-

pounds, $C_{10}F_{18}$ (from naphthalene) and $C_{11}F_{20}$ (from 2-methylnaphthalene). The physical properties of some of these compounds have been described by Grosse and Cady (*Ind. Eng. Chem.*, 1947, **39**, 367) and by Fowler *et al.* (*ibid.*, p. 375), and physical properties at 25° have been quoted in our earlier communications.

The fluorocarbons show remarkable chemical and physical properties which illustrate the abnormally high intramolecular and low intermolecular forces in these compounds. Chemically, they are extremely inert, and do not react with concentrated acids, alkali, oxidising agents, or the majority of chemical reagents. Decomposition with potassium or sodium at 600—700° was used for analysis. Profound degradation occurs when fluorine is passed into a liquid fluorocarbon, but when the fluorine is diluted with nitrogen there is either no reaction or the reaction can be controlled to a certain extent. Perfluoromethyl*cyclo*hexane, for example, can be converted into perfluoro*cyclo*hexane in small yield by treatment with diluted fluorine, thus indicating that the initial attack takes place on the side chains and not on the nucleus. Impure fluorocarbons give polymeric as well as decomposition products. When a fluorocarbon is mixed with fluorine diluted by nitrogen and passed through a heated tube, degradation to fluorocarbons of lower molecular weight occurs. Reaction with cobalt trifluoride at high temperatures also brings about carbon–carbon bond fission. The fluorocarbons are thermally very stable, and perfluoromethyl*cyclo*hexane, for example, underwent little decomposition at 550°. Prolonged heating at 550—700° brought about partial decomposition to fluorocarbons of lower molecular weight with the deposition of carbon.

The effect of fluorine on the boiling point of a hydrocarbon is quite different from that observed with the other halogens. The introduction of one fluorine atom almost invariably raises boiling point, a notable exception being the replacement of nuclear hydrogen in an aromatic compound. Subsequent introduction of fluorine leads to a further increase in boiling point until a maximum is reached, after which the boiling points of the fluoro-derivatives steadily fall to a minimum when all hydrogen atoms have been replaced by fluorine and all double bonds saturated by fluorine (*e.g.*, methyl*cyclo*hexane, b. p. 101°, trifluoromethyl*cyclo*hexane, b. p. 107°, perfluoromethyl*cyclo*hexane, b. p. 76°). The boiling point of a fluorocarbon containing more than five carbon atoms is lower than that of the corresponding hydrocarbon and the difference in boiling point increases with higher members of the series. The boiling points of fluorocarbons are recorded in Table II. Those of isomeric fluorocarbons are very similar, and perfluoro-1 : 2-, -1 : 3-, and -1 : 4-dimethyl*cyclo*hexane and perfluoroethyl*cyclo*hexane, for example, all boil in the range 101—103°. It is not surprising to find that the empirical relationships which have been used to correlate the boiling point and structure of hydrocarbons (*e.g.*, Lautié, *Bull. Soc. chim.*, 1940, **7**, 685: Nekraskov, *Z. physikal. Chem.*, 1929, *A*, **141**, 378; 1930, *A*, **148**, 216) hold equally well or even better for the fluorocarbons.

The introduction of fluorine into an organic compound gives a product of higher density than the starting material, and in this respect fluorine resembles the other halogens. The density–temperature graphs for the fluorocarbons (cf. Table III) are linear and almost parallel for the higher members of the series. The molecular volumes of the fluorocarbons calculated from extrapolated densities at the boiling point are shown in Table IV.

The refractive indices of the fluorocarbons are shown in Table V; fluorine reduces the refractive index relative to the parent hydrocarbon. The refractive indices of the fluorocarbons are the lowest recorded for organic compounds of comparable complexity. The temperature coefficient for refractive index is approximately 0·0004 for all the fluorocarbons examined.

It appears that the specific refraction of a homologous series is characteristic and almost constant for the series—0·09625 for the perfluoroparaffins, 0·0971 for the monocyclic fluorocarbons, and 0·0997 for the bicyclic fluorocarbons (Table VI). The specific refraction is independent of temperature over the ranges measured.

The atomic refraction of fluorine is 1·220 for the mono- and bi-cyclic fluorocarbons; in the perfluoroparaffins, it slowly decreases with ascent of the series, with an average value of *ca.* 1·255 (Table VI, cf. Grosse and Cady, *loc. cit.*; Fowler *et al.*, *loc. cit.*). Thus the atomic refraction of fluorine varies with the type of compound. Henne (*J. Amer. Chem. Soc.*, 1936—1949), Grosse, Wackher, and Linn (*J. Physical Chem.*, 1940, **44**, 275) and Swarts (*J. Chim. physique*, 1923, **20**, 30) have found values of AR_F from 0·90 to 1·10 in diverse partially fluorinated paraffins.

If it is known to which homologous series (paraffin, monocyclic, or bicyclic) a partially fluorinated compound, $C_xH_yF_z$, containing only carbon, hydrogen, and fluorine belongs, then its degree of fluorination (the ratio of number of fluorine atoms to the total number of atoms other than carbon) can be estimated from measurements of refractive index and density, taking

$AR_C = 2{\cdot}418$, $AR_H = 1{\cdot}100$, and the appropriate value for AR_F. The procedure can be extended to the relation between specific refraction and degree of halogenation for chlorofluorohydrocarbons. Refractometric analysis of this type is most accurate for compounds with a high degree of halogenation and is particularly useful in estimating the hydrogen content of the compound.

The viscosities of the fluorocarbons are greater than those of the corresponding hydrocarbons but very much less than those of chlorinated compounds with a similar degree of halogenation. The large change in viscosity with temperature for the fluorocarbons (see Tables VII and VIII) again indicates the low order of magnitude of the intermolecular forces. The fluidity ($1/\eta$)–temperature curves tend to linearity at higher temperatures but, when $\log \eta$ is plotted against the reciprocal of absolute temperature, a more strictly linear relationship is found. The variation of viscosity with temperature for the fluorocarbons may therefore be represented by an equation of the type $\log \eta = B/T - A$, which is equivalent to the expression $\eta = C/Ke^{BT}$ derived by Andrade (*Phil. Mag.*, 1934, **17**, 497, 698) where K and C are constants. Values of A and B are recorded in Table IX. It is interesting that there is a marked difference in viscosity between a perfluoroparaffin and a mono- or bi-cyclic compound with the same number of carbon atoms. This is particularly noticeable at the lower temperatures (*e.g.*, C_7F_{14} shows η^{25} 15·6 while C_7F_{16} shows η^{25} 9·15; $C_{10}F_{18}$ shows η^{25} 51·4 while $C_{10}F_{20}$ has η^{25} 29·5). Molecular structure is clearly a major factor in determining viscosity and consequently viscosity can be used to distinguish fluorocarbons having the same number of carbon atoms but different carbon skeletons.

Introduction of one fluorine atom into a hydrocarbon causes an increase in the surface tension. Further fluorination causes initially an increase, and later a decrease, in the surface tension, and in this respect the change in surface tension is analogous to the change produced in the boiling point by progressive fluorination (*e.g.*, γ^{20} for C_6H_{14} 18·4, $C_6H_{13}F$ 21·8, $C_6H_5{\cdot}CH_3$ 28·5, $C_6H_5{\cdot}CF_3$ 23·4, $C_6F_{11}{\cdot}CF_3$ 14·2). The surface tensions of the fluorocarbons are lower than those of other organic compounds of a similar molecular complexity and vary linearly with temperature (see Table X).

The parachors of the fluorocarbons vary only slightly ($\pm$ 0·5%) with temperature, the maximum deviation occurring as might be expected at temperatures near the boiling point.

The average value of P_{CF_2} (see Table XI) for the perfluoroparaffins and the perfluoro-cyclic compounds is 53·7, whence P_F is 22·55. The values of P_F in Table XI calculated by assuming that there is no constitutional parachor for the ring systems show that there is good agreement within a particular homologous series with only slight differences between the alicyclic, monocyclic, and bicyclic compounds.

The value of P_F derived from the fluorocarbons is much lower than any previously put forward from measurements on other organic fluorides. Sugden (" Parachor and Valency ") suggested 25·0 and Mumford and Phillips (*J.*, 1929, 2112) 25·5, while Desreux (*Bull. Soc. chim. Belg.*, 1935, **44**, 249) used 26·3, 24·2, or 25·1 when fluorine was present in an aliphatic, trifluoromethyl, or an aromatic compound respectively.

Experimental.

Purification of Fluorocarbons.—The crude fluorocarbons obtained by the methods described in Parts III—V were extracted with cold absolute ethanol to remove fluorohydrocarbons, and after being washed with water and dried were either passed over cobalt trifluoride at 350° or, more usually, treated with uranium hexafluoride at 100°, at the boiling point or under pressure. After removal of uranium hexafluoride, washing, and drying, the fluorocarbons were distilled through an efficient fractionating column. Middle fractions were taken for the measurement of physical properties, each of which is the average of at least two determinations with fresh samples.

Chemical Properties of the Fluorocarbons.—Only typical experiments are described.

Reaction with acids. Perfluorodimethyl*cyclo*hexane (30 g.) did not react with concentrated sulphuric acid (100 ml.) during 5 hours at room temperature or later during 4 hours under reflux. Similar results were observed with fuming nitric acid, concentrated potassium permanganate solution, or chromic acid.

Reaction with alkali. Perfluorononane (25 g.) was unaffected overnight by 50% sodium hydroxide solution or when later heated under reflux for 5·5 hours.

Reaction with fluorine in the liquid phase. After perfluorodimethyl*cyclo*hexane (30 g.), stirred rapidly, had been treated with fluorine (5 g./hr.) diluted with nitrogen (10 l./hr.) for 5 hours, the residue (22·1 g.) was mainly unchanged, with a trace of more volatile material.

Perfluoromethyl*cyclo*hexane (21 g.) treated with fluorine (10 g./hr.) diluted with nitrogen (7 l./hr.) yielded perfluoro*cyclo*hexane (0·2 g.), unchanged perfluoromethyl*cyclo*hexane (14·2 g.), and volatile products. Impure fluorocarbons gave polymeric as well as decomposition products on treatment with

fluorine diluted with nitrogen, whilst the passage of undiluted fluorine into fluorocarbons caused inflammation and some deposition of carbon.

Reaction with fluorine in the vapour phase. Perfluorodimethyl*cyclo*hexane and fluorine (diluted by equal volume of nitrogen) were introduced through diametrically opposite tubes in a horizontal unpacked steel reaction vessel 34" long and 3" in diameter, and the products condensed and distilled. The results are summarised in Table I.

TABLE I.

Temp.	50°	50°	100°	120°	160°
C_8F_{16} (ml./hr.)	4	2	3	2·5	2
F_2 (g./hr.)	6	5	5	7	8
C_8F_{16} recovered, %	74	60	62	52	34

Reaction with cobalt trifluoride. Perfluorononane (21·0 g.) was passed over cobalt trifluoride at 550° to yield material (8·4 g.) of b. p. <125° produced by decomposition.

Reaction in a hot tube. Perfluoromethyl*cyclo*hexane was passed rapidly through a nickel tube furnace at 550° with no change in physical properties. Prolonged heating at this temperature caused partial decomposition with deposition of carbon. Carbon tetrafluoride was the main decomposition product although small amounts (*ca.* 10%) of C_2F_6, C_3F_8, etc., were also present.

Boiling Point, Melting Point, and Freezing Point.—Accurate and corrected b. p.s and approx. f. p.s are recorded in Table II. Perfluoro-decane, -undecane, -dodecane, and -hexadecane were recrystallised from carbon tetrachloride.

TABLE II.

Fluoroparaffin.	C_7F_{16}.	C_8F_{18}.	C_9F_{20}.	$C_{10}F_{22}$.	$C_{11}F_{24}$.	$C_{12}F_{26}$.	$C_{16}F_{34}$.
B. p.	82·2°	103·3°	125·3°	144·2°	161°	178°	232°
M. p. or f. p.	−55°	−65°	−16°	36°	57°	75°	125°
Monocyclic.	C_6F_{12}.	C_7F_{14}.	C_8F_{16}.	C_9F_{18}.	$C_{10}F_{20}$.		
B. p.	52·0°	76·2°	101·5°	124·6°	146·5°		
M. p. or f. p.	51°	−37°	−55°	−56°	−44°		
Dicyclic.	$C_{10}F_{18}$.	$C_{11}F_{20}$.					
B. p.	141·9°	160·5°					
M. p. or f. p.	−14°	−40°					

Application of Lautié's expression (*loc. cit.*), $T_b^2 = An + B$ [where T_b is the boiling point (°K.), A and B are constants, and n is the number of carbon atoms in the compound] to the perfluoroparaffins gives $A = 15{,}400$ and $B = 19{,}000$, and satisfactory agreement with the experimental values. The mono- and bi-cyclic fluorocarbons have $A = 18{,}000$ $B = -3{,}900$, and $A = 15{,}800$, $B = 14{,}000$ respectively.

Nekrasov's expression (*loc. cit.*), which can be reduced to that of Lautié, can also be applied with some success to the fluorocarbons. In this equation, $T_b = KM^{1/3}/R$, where K is a constant, M is the molecular weight, and R is the molecular refraction, use of 2·418 and 1·220 (see Table V) for the atomic refraction of carbon and fluorine respectively, leads to a value of 1·700 ± 0·006 for K for the perfluoroparaffins. The expression may then be used to calculate the b. p.s of the fluorohydrocarbons, but the absence of data for fully-characterised fluorohydrocarbons prevents comparison of calculated and observed values.

Density.—Standard methods were used with pyknometers of *ca.* 6·5-ml. and 1·5-ml. capacity. Water- and liquid paraffin-thermostats were used, with temperature control to ±0·05°. Readings were taken at 5 or 6 temperatures in the range indicated in each case and showed a linear relationship between density and temperature. The results are most conveniently recorded therefore in the form $d_4^T = A - BT$ where A and B are constants and T is the temperature (°c.). The data are recorded in Table III. Values of 0·0023 and 0·0027 g./c.c. deg. for the value $B(\mathrm{d}d/\mathrm{d}T)$ have been recorded by Cady *et al.* (*loc. cit.*) for perfluoro-1 : 3 : 5-trimethyl*cyclo*hexane and perfluoro-*n*-heptane respectively.

Kopp suggested that the molecular volumes of hydrocarbons calculated from the densities at the b. p.s are additive in character, and derived a value of 11·0 for the molecular volume of carbon. The molecular

TABLE III.

	A.	*B.*	Temp. range.		*A.*	*B.*	Temp. range.
Monocyclic.				*Fluoroparaffin.*			
C_7F_{14}	1·858	0·00284	0—60°	C_7F_{16}	1·801	0·00240	0—60°
C_8F_{16}	1·897	0·00271	0—60	C_8F_{18}	1·839	0·00251	0—60
C_9F_{18}	1·948	0·00231	0—60	C_9F_{20}	1·860	0·00248	0—60
$C_{10}F_{20}$	1·959	0·00231	0—60	$C_{10}F_{22}$	1·873	0·00230	35—60
				$C_{11}F_{24}$	1·919	0·00248	60—130
Dicyclic.				$C_{12}F_{26}$	1·961	0·00256	80—175
$C_{10}F_{18}$	1·979	0·00232	0—70				
$C_{11}F_{20}$	2·001	0·00222	0—70				

volumes of the fluorocarbons shown in Table IV are calculated from the densities at the b. p.s derived by extrapolation from the data in Table III. The plots of molecular volume at the b. p. against the number of carbon atoms in the fluorocarbon are slightly curved for the perfluoroparaffins and cyclic fluorocarbons, and the molecular volume of fluorine, calculated on the assumption that the molecular volume of carbon in these compounds is 11·0, increases from 10·3 to 11·7 and from 9·5 to 9·9 in the two series. Substantial errors may be involved in the extrapolation to the b. p. of the density–temperature curves.

Refractive Index.—The refractive indices of the fluorocarbons are recorded in Table V in the form $n_D^T = A - BT$ where T is in °c. The refractive index was measured at 10—15 different temperatures in each case. An Abbé refractometer with a special scale was used, and gave readings accurate to ±0·0005 in the region below 1·3000. The value of dn_D/dT is *ca.* −0·00040 for all the fluorocarbons examined.

TABLE IV.

Compound.	C_7F_{16}.	C_8F_{18}.	C_9F_{20}.	$C_{10}F_{22}$.	$C_{11}F_{24}$.	$C_{12}F_{26}$.
Mol. vol. at b. p.	242·1	277·2	314·9	350·8	387·5	425·0
Compound.	C_7F_{14}.	C_8F_{16}.	C_9F_{18}.	$C_{10}F_{20}$.	$C_{10}F_{18}$.	$C_{11}F_{20}$.
Mol. vol. at b. p.	213·3	242·2	271·2	308·7	280·8	311·5

TABLE V.

	A.	*B*.	Temp. range.		*A*.	*B*.	Temp. range.
Monocyclic.				*Fluoroparaffin.*			
C_7F_{14}	1·2865	0·00042	0—40°	C_7F_{16}	1·2770	0·00040	0—40°
C_8F_{16}	1·2935	0·00042	0—60	C_8F_{18}	1·2820	0·00040	0—40
C_9F_{18}	1·3035	0·00038	0—70	C_9F_{20}	1·2865	0·00042	0—50
$C_{10}F_{20}$	1·3060	0·00038	0—65	$C_{10}F_{22}$	1·2890	0·00040	35—60
				$C_{11}F_{24}$	1·2960	0·00040	60—80
Dicyclic.							
$C_{10}F_{18}$	1·3185	0·00040	0—70				
$C_{11}F_{20}$	1·3215	0·00038	0—70				

TABLE VI.

	r.	$[M_R]$.	AR_F.		*r*.	$[M_R]$.	AR_F.
Monocyclic.				*Fluoroparaffin.*			
C_7F_{14}	0·09694	33·93	1·214	C_6F_{16}	0·09618	42·13	1·266
C_8F_{16}	0·09712	38·86	1·220	C_9F_{20}	0·09621	46·21	1·259
C_9F_{18}	0·09714	43·71	1·220	$C_{10}F_{22}$	0·09625	51·78	1·255
$C_{10}F_{20}$	0·09721	48·61	1·221	$C_{11}F_{24}$	0·09634	56·65	1·252
Dicyclic.							
$C_{10}F_{18}$	0·0998	46·14	1·220				
$C_{11}F_{20}$	0·0997	51·00	1·220				

The values for the specific refraction r shown in Table VI have been calculated from the Lorentz–Lorenz expression using n_D^{25}, the molecular refraction $[M_R]$ and the atomic refraction of fluorine AR_F were derived by using the Eisenlohr value of 2·418 for the atomic refraction of carbon.

The values of n_D^{25} and d_4^{25} for $C_{10}F_{22}$ and $C_{11}F_{24}$ were extrapolated. Fowler *et al.* (*loc. cit.*) quote a value for AR_F of 1·24—1·25 for both perfluoroparaffins and perfluoromonocyclic hydrocarbons.

Viscosity.—The viscosity (millipoises) of the fluorocarbons, determined in standard Ostwald viscometers, are recorded in Tables VII and VIII. The variation in viscosity with temperature is conveniently expressed in the form $\log \eta = (B/T) - A$ and values of B and A are recorded in Table IX.

TABLE VII.

Temp.:	25°.	30°.	35°.	45°.	60°.	70°.	80°.	90°.
Monocyclic.								
C_7F_{14}	15·6	14·1	12·8	10·6	8·11	6·98	—	—
C_8F_{16}	19·3	17·4	15·8	13·2	10·2	—	—	—
C_9F_{18}	22·4	20·0	18·3	15·1	11·7	—	—	—
$C_{10}F_{20}$	29·5	26·1	23·3	18·6	13·5	—	—	—
Dicyclic.								
$C_{10}F_{18}$	51·4	42·9	37·6	28·6	19·6	15·8	12·6	—
$C_{11}F_{20}$	53·6	—	39·9	30·6	20·7	16·8	13·4	11·0

R R

Surface Tension and Parachor.—The surface tension was determined by Sugden's maximum bubble-pressure method (*J.*, 1922, 864; *J.*, 1924, 27), improved according to Quayle and Smart (*J. Amer. Chem. Soc.*, 1944, **66**, 937; 1945, **67**, 21) and by Desreux (*loc. cit.*). The surface tensions of the fluorocarbons are extremely low, and precautions were taken to exclude dust, grease, etc. Where possible a different and freshly distilled sample of the fluorocarbon was used for each determination. The surface tension of each fluorocarbon was determined for at least five different temperatures. In each case the surface tension

TABLE VIII.

Temp.:	25°.	30°.	35°.	45°.	60°.	70°.	80°.	85°.	90°.	95°.
Perfluoroparaffins.										
C_7F_{16}	9·15	8·31	7·69	6·61	—	—	—	—	—	—
C_8F_{18}	14·9	13·6	12·4	10·4	8·12	7·07	—	—	—	—
C_9F_{20}	18·1	16·3	14·7	12·2	9·15	—	—	—	—	—
$C_{10}F_{22}$	—	—	20·5	16·4	12·0	10·0	8·37	—	—	—
$C_{11}F_{24}$	—	—	—	—	16·4	13·5	11·1	—	9·38	—
$C_{12}F_{26}$	—	—	—	—	—	—	13·1	11·9	10·8	10·0

TABLE IX.

Fluorocarbon.	C_7F_{16}.	C_8F_{18}.	C_9F_{20}.	$C_{10}F_{22}$.	$C_{11}F_{24}$.	$C_{12}F_{26}$.
B	641·8	733·2	839·7	938·3	976·1	1001
A	1·1978	1·2871	1·5602	1·7351	1·7167	1·7195

Fluorocarbon.	C_7F_{14}.	C_8F_{16}.	C_9F_{18}.	$C_{10}F_{20}$.	$C_{10}F_{18}$.	$C_{11}F_{20}$.
B	775·0	763·0	782·1	940·8	1147	1127
A	1·4142	1·2800	1·2804	1·6889	2·1478	2·0588

TABLE X.

Fluorocarbon.	C_7F_{14}.	C_8F_{16}.	C_9F_{18}.	$C_{10}F_{20}$.	$C_{10}F_{18}$.	$C_{11}F_{20}$.
γ_0	15·85	17·02	19·10	19·57	20·36	21·17
K	0·0840	0·0806	0·0774	0·0814	0·0834	0·0804

Fluorocarbon.	C_8F_{18}.	C_9F_{20}.	$C_{10}F_{22}$.	$C_{11}F_{24}$.	$C_{12}F_{26}$.
γ_0	15·52	16·34	16·68	17·47	18·23
K	0·0711	0·0766	0·0700	0·0665	0·0665

TABLE XI.

Fluorocarbon.	C_7F_{14}.	C_8F_{16}.	C_9F_{18}.	$C_{10}F_{20}$.	$C_{10}F_{18}$.	$C_{11}F_{20}$.
P	377·3	431·4	484·9	538·1	497·1	550·8
P_{CF_2}	53·2	53·5	54·1		53·7	
P_F	22·65	22·66	22·64	22·61	22·83	22·81

Fluorocarbon.	C_8F_{18}.	C_9F_{20}.	$C_{10}F_{22}$.	$C_{11}F_{24}$.	$C_{12}F_{26}$.
P	474·7	528·4	582·5	636·3	690·0
P_{CF_2}	53·7	54·1	53·8	53·7	
P_F	22·55	22·55	22·57	22·57	22·57

varied linearly with temperature and is best expressed in the form $\gamma_T = \gamma_0 - KT$, where γ_0 is the surface tension at 0° and T is the temperature in °c., which must be above the m. p. of the compound. Values of γ_0 (dynes/cm.) and K are shown in Table X. The values of γ_0 for $C_{10}F_{22}$, $C_{11}F_{24}$, and $C_{12}F_{26}$ have been derived by extrapolation.

The parachors (P) of the fluorocarbons, the increment in parachor for a $-CF_2-$ group (P_{CF_2}) for successive members of a homologous series, and the atomic parachor of fluorine (P_F) calculated from the above data are shown in Table XI. The atomic parachor of carbon was taken as 8·6, the value derived by Vogel *et al.* (*J.*, 1934, 333; 1943, 636; 1946, 133).

The authors are indebted to (the late) Sir Norman Haworth, F.R.S., and to Professor M. Stacey, F.R.S., for their interest in this work during the period 1940—46, and thank the Director-General of Scientific Research of the Ministry of Supply for permission to publish it.

THE CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM.

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130. *Organic Fluorides. Part VII. Co-ordination Compounds of Fluoroacetylacetones.*

By R. N. Haszeldine, W. K. R. Musgrave, F. Smith, and (Miss) L. M. Turton.

Mono-, tri-, and hexa-fluoro-derivatives of acetylacetone have been prepared by a Claisen type of condensation. Only the hexafluoro-derivative, where two CH_3 groups have been replaced by CF_3 groups, show properties which differ greatly from those of the parent acetylacetone.

Certain co-ordination compounds have been made and their absorption spectra determined. The uranous complexes with trifluoroacetylacetone and hexafluoroacetylacetone can be sublimed *in vacuo* without decomposition.

The acetylacetone complexes of many metals are volatile (Morgan and Moss, *J.*, 1914, **105**, 189) and certain of the acetylacetone derivatives of bivalent metals can be distilled without decomposition. The uranyl acetylacetone complex is stable but cannot be sublimed or distilled without decomposition, and although the uranous derivative is more volatile it slowly decomposes when heated. Since greater volatility and increased stability result from the introduction of several fluorine atoms into an organic molecule, the fluoroacetylacetone derivatives of uranium were examined in the hope that these might prove to be stable and volatile without decomposition.

Monofluoroacetylacetone was made by condensing ethyl monofluoroacetate with acetone in the presence of sodium. Similarly ethyl trifluoroacetate with acetone yielded trifluoroacetylacetone, and with trifluoroacetone (Swarts, *Bull. Acad. Roy. Belg.*, 1927, **13**, 175) gave hexafluoroacetylacetone (Miss L. M. Turton, Thesis, Birmingham, 1945). Since this work was completed, the synthesis of tri- and hexa-fluoroacetylacetone by a similar method has been described (Henne, Newman, Quill, and Staniforth, *J. Amer. Chem. Soc.*, 1947, **69**, 1819; Reid and Calvin, *ibid.*, 1950, **72**, 2948). The condensation proceeded most vigorously between ethyl trifluoroacetate and acetone, and with ethyl monofluoroacetate was comparable in vigour to that with ethyl acetate. That of trifluoroacetone with ethyl trifluoroacetate was much less vigorous.

There is a marked difference between mono- and tri-fluoroacetylacetone on the one hand and hexafluoroacetylacetone on the other. It was expected that the monofluoroacetylacetone would not differ very much from acetylacetone but it seemed likely that the trifluoroacetylacetone would show some of the peculiarities of the hexafluoroacetylacetone. In fact the trifluoro-compound behaved more like the unsubstituted acetylacetone.

Mono- and tri-fluoroacetylacetone boil at about the same temperature (105° approx.). This is rather surprising since, by analogy with the hydrofluorocarbons (Grosse and Cady, *Ind. Eng. Chem.*, 1947, **39**, 367; Fowler *et al.*, *ibid.*, p. 375), the introduction of one fluorine atom might be expected to increase the boiling point above that of acetylacetone (137°). Since hexafluoroacetylacetone boils at about 64° (cf. Henne *et al.*, *loc. cit.*) it appears that although the intermolecular forces are modified by replacing hydrogen by fluorine in each methyl group the factor influencing the boiling point is whether one or both methyl groups are involved.

The tendency of the fluoroacetylacetones to form hydrates increases as the number of fluorine atoms increases. Thus the more highly fluorinated hexafluoroacetylacetone crystallised as a hydrate even on exposure to air, and co-ordination of it with metals could be effected only in anhydrous media. Further, while acetylacetone is soluble in eight parts of water, hexafluoroacetylacetone is miscible with water in all proportions.

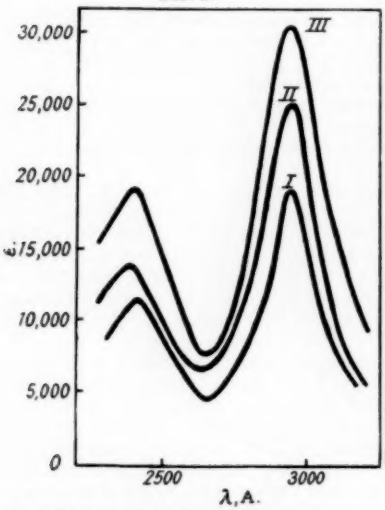
Monofluoroacetylacetone readily afforded crystalline copper and iron co-ordination compounds. Trifluoroacetylacetone gave copper, iron and uranyl compounds by the usual procedure (cf. Biltz and Clinch, *Z. anorg. Chem.*, 1904, **40**, 220). While the uranous co-ordination compound could be made in aqueous solution the best yields were obtained under anhydrous conditions by allowing the trifluoroacetylacetone to react with uranium tetrachloride in an inert solvent in the presence of sodium. Hexafluoroacetylacetone failed to give co-ordination compounds in aqueous solution, no doubt because the compound reacts more readily with water than with metal ions. However, under the anhydrous conditions used for making the corresponding co-ordination compounds of trifluoroacetylacetone it readily formed a copper and a uranous compound (cf. Schultz and Larsen, *J. Amer. Chem. Soc.*, 1949, **71**, 3250).

Spectrophotometric examination showed that hexafluoroacetylacetone existed in the enolic

modification to a much greater extent than was the case with either acetylacetone or hexabromoacetylacetone (cf. Reid and Calvin, *loc. cit.*).

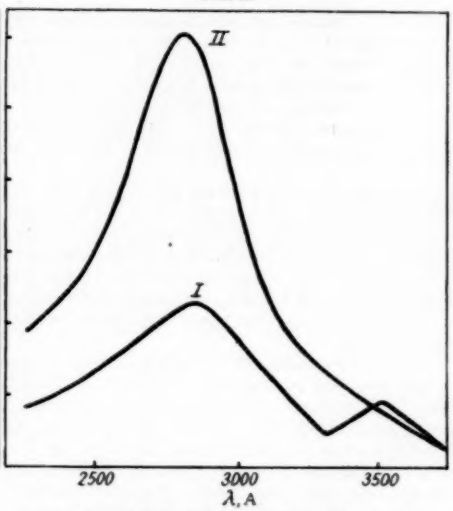
The ultra-violet absorption spectra of some co-ordination compounds of the fluoroacetylacetones, in ethanol, are shown in Figs. 1, 2, and 3, and the absorption maxima are recorded in the table.

FIG. 1.



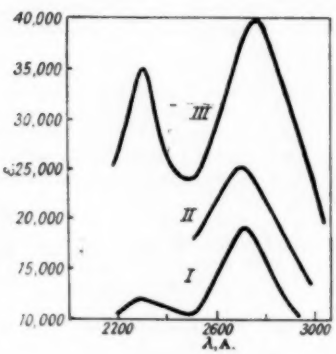
I. *Cupric derivative of acetylacetone.*
II. *Cupric derivative of monofluoroacetylacetone.*
III. *Cupric derivative of trifluoroacetylacetone.*

FIG. 2.



I. *Uranyl derivative of trifluoroacetylacetone.*
II. *Uranous derivative of trifluoroacetylacetone.*

FIG. 3.



I. *Ferric derivative of acetylacetone.*
II. *Ferric derivative of monofluoroacetylacetone.*
III. *Ferric derivative of trifluoroacetylacetone.*

Absorption maxima of co-ordination compounds.

	Cu.		Fe.		U.		UO_2.	
	λ.	ε.	λ.	ε.	λ.	ε.	λ.	ε.
Acetylacetone	2420	11,400	2290	12,000	—	—	—	—
	2950	19,000	2710	19,000	—	—	—	—
Fluoroacetylacetone	2400	14,000	2700	25,000	—	—	—	—
	2940	25,000	—	—	—	—	—	—
Trifluoroacetylacetone ...	2400	19,500	2300	30,000	2800	30,000	2860	11,500
	2940	31,000	2760	40,000	—	—	3520	4,500

Experimental.

Fluoroacetylacetone.—Dry acetone (25 c.c.) was added to fluoroacetic ester (20 g.) in the presence of sodium wire (5 g.), the mixture being cooled in an ice–salt bath. No apparent reaction occurred at this temperature but on removal of the cooling mixture the solution became red and after it had been kept overnight at room temperature all the sodium had dissolved. The usual methods failed to produce a copper derivative which would have facilitated purification, and hence the reaction mixture was diluted with water and the ethereal layer separated and washed once with water. The washings were combined with the aqueous layer and washed once with ether to remove any unchanged ester. On acidification of the aqueous solution with acetic acid, the colour changed from red to yellow. The solution now gave the typical red-purple colour with dilute ferric chloride but no insoluble copper derivative was produced (cf. Henne *et al.*, *loc. cit.*). The aqueous layer was acidified with dilute sulphuric acid and extracted with ether. The ethereal layer, which reacted acid after being washed with water, was dried and distilled, giving fluoroacetylacetone (5 g.), b. p. *ca.* 25°/15 mm. The diketone so obtained formed a blue-mauve cupric derivative which crystallised well from ethyl alcohol. The ferric derivative, prepared in the usual way, also crystallised from ethyl alcohol; it was readily soluble in ether.

Trifluoroacetylacetone.—To ethyl trifluoroacetate (74·5 g.) and sodium wire (10 g.) in ether (5 c.c.) at 0°, dry acetone (80 ml.) was added at such a rate as to maintain a steady reaction. After 2 hours at 0° the mixture was allowed to warm to room temperature. Ice-water (50 ml.) was added to the reddish-brown mixture. The aqueous layer was made slightly acid with acetic acid and the cupric trifluoroacetylacetone complex (see below) was precipitated by the addition of an excess of a warm saturated solution of cupric acetate. After being kept overnight at 0° the copper derivative was filtered off and dissolved in ether. The ethereal solution, after being shaken with 2N-sulphuric acid and then with water, was dried (Na_2SO_4) and distilled, giving trifluoroacetylacetone, b. p. 105°, n_D^{20} 1·379 (62%) (Found: C, 38·9; H, 3·0; F, 36·7. Calc. for $C_5H_5O_2F_3$: C, 39·0; H, 3·2; F, 37·0%). Henne *et al.* (*loc. cit.*) and Reid and Calvin (*loc. cit.*) record b. p. 107°.

When trifluoroacetylacetone was shaken with a saturated solution of copper acetate a light-blue precipitate of the cupric derivative was obtained which crystallised from alcohol as long blue needles (Found: F, 30·5; Cu, 16·9. Calc. for $C_{10}H_4O_4F_6Cu$: F, 30·8; Cu, 17·2%).

Trifluoroacetylacetone, shaken with concentrated ferric chloride in the presence of sodium acetate, gave the *ferric* compound as red crystals which separated well from alcohol (Found: F, 32·7; Fe, 10·7. $C_{15}H_{12}O_6F_9Fe$ requires F, 32·2; Fe, 10·9%).

Trifluoroacetylacetone was shaken with a solution of uranyl nitrate made slightly alkaline with aqueous sodium carbonate; the orange-yellow *uranyl* compound so formed recrystallised from dioxan, ether, or benzene (Found: C, 20·6; H, 1·6; F, 19·4; U, 40·7. $C_{10}H_6O_8F_6U$ requires C, 20·8; H, 1·4; F, 19·8; U, 41·3%). When heated at 160°/10^{-4} mm., the product decomposed with the production of trifluoroacetylacetone.

(*a*) To a solution of uranyl acetate (10 g.) in water (50 c.c.) sodium dithionite (7 g.) was added. The precipitate was dissolved in concentrated hydrochloric acid, kept for 24 hours, and filtered to remove a little sulphur. Dilute aqueous sodium hydroxide was then added to neutralize most of the acid and this was followed by trifluoroacetylacetone (10 g.) and more sodium hydroxide until vigorous shaking produced a khaki-green precipitate (5 g.) of the *uranous* compound (needles from alcohol, cubic crystals from benzene). These operations were carried out in an atmosphere of nitrogen. (*b*) The trifluoroacetylacetone (1 g.) in ether was added to uranium tetrachloride (2 g.) and sodium wire (2 g.). A reaction occurred and the solution became khaki-green. When the reaction subsided, the ethereal solution was decanted and concentrated in an atmosphere of nitrogen. The residual uranous compound (1 g.) was purified by sublimation or crystallisation. The crystals sublimed at 100—110°/10^{-4} mm. without decomposition and without leaving any residue (Found: C, 28·0; H, 2·0; F, 26·5; U, 26·5, 27·3. $C_{20}H_{16}O_8F_{12}U$ requires C, 28·0; H, 1·9; F, 26·8; U, 28·0%).

Hexafluoroacetylacetone.—Trifluoroacetone was prepared by Swarts's method (*Bull. Acad. Roy. Belg.*, 1927, **13**, 175) from ethyl trifluorosodioacetoacetate. [Ethyl trifluoroacetoacetate showed two bands in *cyclo*hexane: at 2380 (ε = 3000 approx.) and 2880 A. (ε = 400 approx.).] Its copper derivative showed bands at 2200 (ε = 11,000 approx.) and 2700 A. (ε = 21,000 approx.) (*c* = 3·0 mg.% in ethanol). Ethyl trifluorosodioacetoacetate was decomposed with hot (80—90°) dilute sulphuric acid in an all-glass apparatus, to give trifluoroacetone which was condensed in dry ether at −78°. The ethereal solution was dried ($MgSO_4$ or $CaCl_2$) and distilled, the trifluoroacetone being condensed in dry ether at −78°.

To sodium wire (7·8 g.) covered with dry ether, ethyl trifluoroacetate (37·8 g.) was added with cooling (0°). A dry ethereal solution of trifluoroacetone prepared by Swarts's method from 60 g. of ethyl trifluoroacetate was then added at −78°. The reaction mixture was allowed to warm to room temperature during 12 hours. Any trifluoroacetone which distilled during this time was condensed and returned to the reaction mixture which was kept overnight at room temperature until all the sodium had dissolved (cf. Henne *et al.*, *loc. cit.*). The reddish-brown mixture was treated with an excess of dilute sulphuric acid and extracted with ether. The combined ethereal extracts were dried (Na_2SO_4) and distilled, giving a liquid (20 g.) which boiled over the range 36—90° (Henne *et al.*, *loc. cit.*, give b. p. 63—64° for this compound). The material distilling between 54° and 85° underwent partial crystallisation which became complete on exposure to air. The portion of b. p. 85—90° crystallised immediately; it appeared to be the dihydrate of hexafluoroacetylacetone (cf. Schulz and Larsen, *loc. cit.*). The crystalline material reacted acid to litmus and Congo-red (Found: C, 24·8; H, 3·0. $C_5H_2O_2F_6.2H_2O$ requires C, 24·6; H, 2·5%).

A crystalline residue left after distilling the hexafluoroacetylacetone had m. p. 97° (after crystallisation from light petroleum). This product was soluble in ether and light petroleum and, unlike hexafluoro-

acetylacetone, it was insoluble in water. The nature and mode of formation of this crystalline compound will be the subject of a later communication.

The crystalline hydrate of hexafluoroacetylacetone showed a band at 3050 A. ($\varepsilon = 80$ approx.) ($c = 116$ mg.% in ether), moving to 2700 A. ($\varepsilon = 100$ approx.) after being kept over phosphoric oxide for 1 hour. When an ethereal solution of the hydrate was kept over sodium for 3 days the solution had a band at 3050 A. ($\varepsilon = 4000$ approx.) ($c = 11{\cdot}6$ mg.%). It seems, therefore, that the anhydrous hexafluoroacetylacetone exists in the enolic modification to a much greater extent than either the parent acetylacetone (see Morton, *J.*, 1934, 898) or even the corresponding hexabromoacetylacetone which shows only an inflection in its absorption curve at 3000 A. ($\varepsilon = 800$ approx.) ($c = 49{\cdot}4$ mg.% in *cyclo*hexane), whereas when it is enolised by dissolution in alcohol containing sodium ethoxide a band appears at 3640 A. ($\varepsilon = 700$ approx.) ($c = 9{\cdot}9$ mg.%).

Hexafluoroacetylacetone failed to give the usual coloured compounds when treated with copper or iron salts in aqueous solution (cf. Henne *loc. cit.*) but when an ethereal solution of the hydrate was kept in contact with anhydrous copper sulphate the latter slowly became blue and the ethereal solution developed an emerald-green colour which showed an absorption band typical of the metallic acetylacetone compounds. Anhydrous hexafluoroacetylacetone gave a deep-red solution when treated in dry ether with anhydrous ferric chloride. The solution deposited red crystals which decomposed on removal of solvent, probably because of hydration of the diketone.

When the diketone reacted with uranium tetrachloride in ether solution in the presence of metallic sodium a brownish-khaki colour developed. Filtration in an inert atmosphere followed by evaporation gave a brownish crystalline residue of $(CF_3{\cdot}CO{\cdot}CH{\cdot}CO{\cdot}CF_3)_3U$ which was purified by sublimation at 40—50°/0·001 mm. The brown crystals, m. p. *ca.* 90°, b. p. 145° (decomp.), could be kept indefinitely in an atmosphere of carbon dioxide but underwent some decomposition when sublimed at 70—80°/0·2 mm.

Repeated attempts to prepare hexafluoroacetylacetone by classical methods (for example, by condensing trifluoroacetoacetic ester with trifluoroacetyl chloride) failed (W. K. R. Musgrave, Thesis, Birmingham, 1943; cf. Breslow *et al.*, *J. Amer. Chem. Soc.*, 1946, **68**, 100, footnote 8).

The authors thank (the late) Professor Sir Norman Haworth, F.R.S., and Professor M. Stacey, F.R.S., for their interest in this work during 1940—46 and Dr. M. G. Webb for a specimen of hexabromoacetylacetone. They also thank the Director General for Scientific Research for permission to publish it.

THE CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM 15. [*Received, October 13th*, 1950.]

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131. *Specification of Configuration about Quadricovalent Asymmetric Atoms.*

By R. S. CAHN * and C. K. INGOLD.

A convention, termed the sequence rule, is proposed whereby the groups a, b, c, and d attached to a quadricovalent asymmetric atom (Xabcd) can be correlated, each to each, with the OH, CHO, $CH_2{\cdot}OH$, and H of glyceraldehyde. According as this correlation leads to dextrorotatory or lævorotatory glyceraldehyde, so the asymmetric atom X is assigned a D- or a L-configuration, and a D or a L symbol is used in the name of the compound. The resulting configurations embrace, as specific cases, previous uses of these prefixes in carbohydrate and amino-acid chemistry; they clarify nomenclature where this has been in dispute, notably when more than one asymmetric atom is present in the molecule, and they provide unambiguous definitions where this was not previously possible. Some representative examples are discussed.

THE most extensive single class of optically active molecules consists of those whose dissymmetry can be completely factorised into the asymmetry of quadricovalent atoms. The configuration of molecules of this class may be fully specified by stating the configuration about each asymmetric atom. The purpose of the present paper is to suggest conventions through which this can be done compactly enough for inclusion in the name of a substance.†

In the present state of knowledge, the most satisfactory procedure is, first, to choose, as

* This paper presents proposals which are not to be construed as already settled editorial policy.

† The following types of dissymmetry can lead to optical activity, but are not covered in this discussion, namely, (1) that due to asymmetric atoms of covalency other than four, for instance, six, (2) that associated with atomic asymmetry depending on configurational differences in the adjoining groups, as in dissymmetry of the inositol type, of the allene type, and of related semicyclic-unsaturated, and spiran types, and (3) that unconnected with atomic asymmetry, as in diphenyl derivatives and other structures which show restricted rotation about single bonds.

" standard substance," a single optically active compound, and to assume a configuration for it; and then to adopt a " correlation rule," that is, a formula by means of which the groups about any asymmetric quadricovalent atom may be severally correlated with those about the asymmetric atom in the molecule of the standard substance.

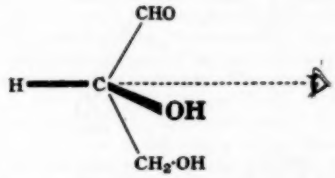
The time will come when absolute configuration can be determined with certainty; and then " standard substance " will be a redundant concept. Anticipating this, we shall express the " correlation rule " in a generalised form, calling it a " sequence rule," so that it can be used without change after the concept of " standard substance " has been discarded. But for the time being we retain this concept.

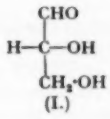
Both in choosing a standard, and in correlating other configurations with it, we are seeking to connect (1) a direction of rotation, (2) a substance, (3) a configurational symbol, (4) a three-dimensional model, and (5) a two-dimensional graphic formula. The last of these is inessential, because the model describes the structure, and the symbol should identify the model; the graphic formula is an additional convenience. The connexion (1)–(2) is established by observation, (2)–(3) by definition, (3)–(4) by an unproven assumption, and (4)–(5) by a convention. None of these determinations can conceivably be taken out of our hands, except the assumption. If, when absolute configurations can be ascertained, that should prove to be wrong, we should still not have to change the configurational symbols: this is what we gain by retaining the concept of " standard substance." But we should have to interchange the models of enantiomers; and we should have either to interchange the two-dimensional formulæ, or to alter the convention by which they are derived from the three-dimensional models.

In order to conform to an already agreed convention, we select glyceraldehyde for the standard substance, but not now as fiducial merely for hydroxy-acids and carbohydrates: we shall seek to describe all configurations that can be expressed entirely in terms of configuration about asymmetric quadricovalent atoms.

In establishing the above connexions for glyceraldehyde itself, C(H)(OH)(CH_2·OH)(CHO), we start with the general concept of dextrorotation, observe that a certain isomer of

FIG. 1.





(I.)

glyceraldehyde has it, define that substance as having the configuration labelled D, assume that its model (represented in Fig. 1) contains the groups OH, CHO, CH_2·OH in clockwise order as viewed from the side remote from H (this being one of four similar and equivalent descriptions *), and agree that this model may be represented by the formula (I). We similarly connect lævorotation with the other isomer, the configuratonal designation L, the enantiomeric model, and the formula with the lateral groups interchanged.

The standard being thus set up, it is necessary next to formulate a rule by which one Group of the four bound to any given asymmetric quadricovalent atom is unambiguously selected for correlation with the Group H of glyceraldehyde, another for correlation with OH, another with CH_2·OH, and the remaining one with CHO. The final step will be to assign to the given asymmetric atom the configurational symbol, D or L, associated with the particular glyceraldehyde produced when each of the four Groups directly bound to the asymmetric atom is replaced by that Group of glyceraldehyde with which it is correlated.

The crux of the present proposal is thus the " rule; " and, as stated above, we prefer to formulate it, not simply as a " correlation rule," but in the generalised form of a " sequence

* The four descriptions result from viewing the model in four tetrahedrally inclined directions. The description given in the text is the most convenient one from which to generalise to other molecules. But another of the four descriptions, namely, that H, OH, CH_2·OH stand clockwise as viewed from the side remote from CHO, is the immediate basis of the projection formula (I). Any of the four descriptions can be reduced to projection formulæ on the usual convention that lines drawn upwards and downwards from the asymmetric atom represent bonds which project behind, and lines drawn to left and right bonds which project in front of, the plane of the diagram. (Naturally, the equivalent representations thus derived are not necessarily interconvertible by rotations in the plane of projection.)

rule," that is, a procedure placing any four different Groups in order. By applying such a rule both to the four Groups bound to the given asymmetric atom, and to the four bound to the asymmetric atom of glyceraldehyde, a one-to-one correlation between the two series of Groups is effected.

The terms Group and Set, written with an initial capital letter, will be used with a definite significance. A Group is an atom or an assembly of atoms bound to the asymmetric atom by a single valency; that is, it is the a, b, c, or d of the Xabcd under consideration. If the asymmetric atom is part of a ring, as in

, there are Groups –ab and –ba containing the same atoms but in a different order. The term Group has then not always the significance normally attached to a "group" in organic chemistry. A Set comprises certain atoms, specified by the rule, which are considered in association when applying the rule.

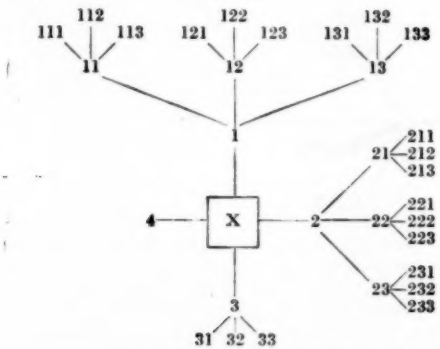
"Sequence rule," or method for ordering Groups bound to a quadricovalent asymmetric atom.

General Procedure.—The Groups are placed in order of decreasing atomic numbers of certain selected Sets of their atoms. These Sets are selected successively by the method, and following as far as is necessary the order of priorities, given hereunder.

Method and Priorities of Selection of Sets of Atoms.—The Sets are selected by reference to a single valency structure of the molecule, that is, one structure containing only localised bonds of integral multiplicity. Methods for the resolution of possible ambiguities in the choice of such a structure are noted later.

(First Set.) To the asymmetric atom let four atoms, 1, 2, 3, and 4 be directly bound. Then the atoms 1, 2, 3, 4 constitute the First Set of atoms.

Fig. 2.



(Second Set.) Let 1 and 2 be any two atoms of identical atomic number in the First Set. To 1 let there be directly bound atoms 11, 12, 13, . . ., here arranged as far as possible in order of decreasing atomic number (see Fig. 2). To 2 let there be directly bound atoms 21, 22, 23, . . ., similarly here arranged. If any of the atoms 11, 12, . . ., 21, 22, . . ., be directly bound to 1 or 2 by a double or triple bond, let that atom be counted twice or thrice, as the case may be, in the series of atoms 11, 12, . . ., or 21, 22, . . . If, after any such augmentation, one of the series of atoms, 11, 12, . . ., and 21, 22, . . ., contains fewer atoms than the other series, let imaginary atoms of atomic number zero be added to the series containing the fewer until each contains the same number of atoms. Then the Second Set contains 11 and 21, unless these have the same atomic number, when it contains instead 12 with 22, unless these also have the same atomic number, when it contains instead 13 and 23, and so on. The complete Second Set of atoms is to be composed by applying the same procedure to every pair of Groups whose atoms of the First Set have identical atomic number.

(Third Set.) Let the atoms 1 and 2 have identical atomic number, and let the atoms 11, 12, . . ., and 21, 22, . . ., be identical in atomic number in pairs, 11 with

21, 12 and 22, and so on throughout. Then the atoms of the Third Set are selected from the atoms 111, 112, . . ., directly bound to atom 11, and the atoms 211, 212, . . ., directly bound to atom 21, as were the atoms of the Second Set from the atoms, 11, 12, . . ., directly bound to atom 1, and the atoms 21, 22, . . ., directly bound to atom 2; unless, however, all the atoms from which the atoms of the Third Set might thus have been selected are identical in atomic number in pairs, each of the series 111, 112, . . ., with one of the series 211, 212, . . ., when the atoms of the Third Set are similarly selected from the atoms 121, 122, . . ., directly bound to atom 12, and the atoms 221, 222, . . ., directly bound to atom 22; and so on. The complete Third Set of atoms is to be composed by generalising the procedure illustrated to every pair of Groups having relationships of identity similar to those assumed for the Groups to which atoms 1 and 2 belong.

(Other Sets.) The method for selection of the $(n + 1)$th Set of atoms is to be developed from that of the nth Set as was that of the Third Set from that of the Second Set.

Supplementary Procedure for taking into Account Dissymmetry dependent on Isotopic Differences.—The General Procedure having failed to yield a complete order of the Groups, it is repeated with respect to those Groups only which are not yet given an unambiguous order, but with the difference that the Groups are now placed in order of decreasing atomic masses of Sets of their atoms selected by the method and according to the priorities specified above.

Conventions for Selection of a Valency Structure.—The sequence rule is formulated on the assumption that the molecule to which it is applied is being represented by a unique valency structure, that is, one structure having all its bonds localised and of integral multiplicity. Since many molecules cannot thus be represented accurately and for all purposes, it becomes necessary to adopt conventions by which a unique valency structure may be assigned to a molecule for the purpose of applying the rule. The following suggested conventions are intended to provide the more obvious necessities of this kind; they do not exhaust every rarely occurring possibility.

(1) Hyperconjugation is neglected. (For example, the bonds of an alkylacetylene or of a propargyl halide are taken as single or triple when applying the sequence rule.)

(2) Participation of atomic *d* orbitals in bonding is neglected; that is, octet structures are adopted whenever possible. (For example, all bonds of the sulphur atoms in sulphoxides and sulphones are taken as single for the purposes of the rule.)

(3) To any mesomeric molecule its usual valency structure is assigned, that is, the structure considered to be most closely related to its normal mesomeric state. (For example, the structure $C{:}C{\cdot}C{:}C$ is assigned to a buta-1 : 3-diene, $Cl{\cdot}C{:}C$ to a vinyl chloride, $C{:}C{\cdot}C{:}O$ to an acraldehyde or a vinyl ketone, $O{:}C{\cdot}OR$ to a carboxylic ester, $O{:}C{\cdot}NR_2$ to a carboxyamide, the non-dipolar two-double-bond structure to a furan or other five-membered aromatic ring compound, and a Kekulé or Kekulé-like structure to any benzene, pyridine, or other six-membered aromatic ring compound.)

(4) When alternative usual valency structures for aromatic molecules exist, one is selected in which the aromatic double bonds are introduced in the way determined by the following procedure. The aromatic ring is considered as composed of chains branching from the point to which is attached the side chain containing the asymmetric atom; these branches are compared according to the priorities of selection set out above, all bonds of the aromatic ring structure being at first counted as single bonds; double bonds of Kekulé type are then inserted into the ring structure starting at, or as close as possible to, the branching point, and proceeding along that branch which according to the priorities of selection would be cited first.

Assignment of Configuration.—The sequence rule places the four Groups bound to the asymmetric atom of glyceraldehyde in the order

$$OH \quad CHO \quad CH_2{\cdot}OH \quad H$$

(for detailed analysis see below). Therefore, if the rule places the four Groups directly bound to a given asymmetric quadricovalent atom in the order

$$\alpha \quad \beta \quad \gamma \quad \delta$$

then α is correlated with the Group OH, β with CHO, γ with $CH_2{\cdot}OH$, and δ with H of glyceraldehyde; and the configurational symbol D or L is assigned to the asymmetric atom in the manner already stated.*

* The case of asymmetric tercovalent atoms could readily be covered by adding to such atoms an imaginary atom of atomic number zero. This would automatically become correlated with the H of glyceraldehyde.

By the assumption made concerning models, the Groups OH, CHO, $CH_2{\cdot}OH$ stand in clockwise order in the model of D-glyceraldehyde, as viewed from the side remote from the H. Therefore, according as the configurational symbol D or L is assigned to the given asymmetric atom, so in the model of the molecule which contains it, α, β, γ will stand in clockwise or counterclockwise order as viewed from the side remote from δ.

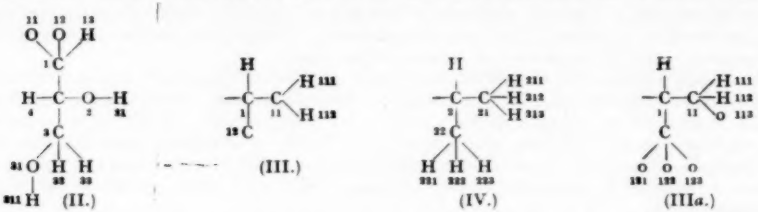
Application of the Priority Conventions.

In principle the sequence rule prescribes that the atoms attached to the asymmetric atom shall be arranged in order of decreasing atomic number, and that, if two or more of them are the same, one " works outwards " until a decision is possible. This simple principle assumes the somewhat involved form of the rule set out above because of the need to define unambiguously how to " work outwards " as the chains ramify. In this section, the procedure will be applied to a few structures chosen to illustrate priority features which may not be obvious at first sight.

Analysis of the simple substance glyceraldehyde according to the rule is represented in (II). Comparison of the First Set gives the order of atoms, 2, (1, 3), 4. Decision between the CHO and the $CH_2{\cdot}OH$ rests on comparison of the Second Set; atom 11 is identical with atom 31, but atom 12 (O) has a higher atomic number than atom 32 (H). The complete sequence, in order of decreasing atomic number, is therefore 2, 1, 3, 4, that is, OH, CHO, $CH_2{\cdot}OH$, H, as stated above.

This example illustrates the representation of a multiple bond (C═O) by single bonds $\left(C\begin{smallmatrix}O\\O\end{smallmatrix}\right)$, but a further point about such representations requires exposition.

Suppose that a decision is required between Groups $-CH_2{\cdot}CH_3$ and $-CH(CH_3)_2$. Analysis gives the structures (III) and (IV). The rule prescribes that one atom attached by a double bond shall be counted twice, in this case the carbon atom of the CH_2 group which appears in (III) as numbers 11 and 12; but this atom only is counted twice, and not also the atoms (H) attached to it. Then, when comparing the Set 11 and 21, or the Set 12 and 22, the valency



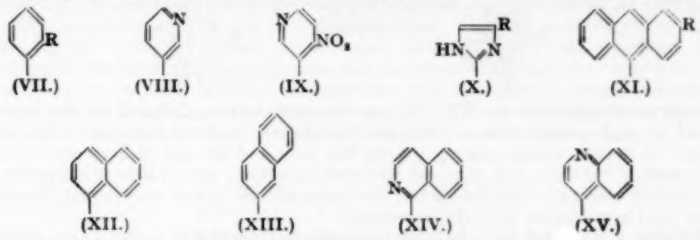
difference must, according to the rule, be compensated by imaginary atoms of atomic number zero, denoted by " o " in (III*a*). The order of decreasing atomic numbers is thus settled at the three-figure Sets: (IV) precedes (III). Imaginary atoms of atomic number zero are also used in other cases, *e.g.*, to establish precedence of $-NO_2$ over $-NO$, of $-NH_3^+$ over $-NH_2$, of $-SO_2H$ over SO_2H, etc.; such priorities would not otherwise have been defined.

In the rule, the atoms 11, 12, 13, . . ., 21, 22, 23, . . ., etc., are arranged in order of decreasing atomic number (second sentence of the paragraph relating to the Second Set), and where necessary the atoms 111, 112, . . ., are compared with the atoms 211, 212, . . . before proceeding to a comparison of 121, 122, . . . with 221, 222, . . . The

necessity for this is best explained by an example such as (V) and (VI). No decision is possible at the Second Set (two-figure numbers). In the Third Set, comparison of 111 with 211 gives the order (V) before (VI), and this is the decision of the rule since atoms 11 and 21 (O) have a higher atomic number than atoms 12 and 22 (C). Without such a provision in the rule, comparison of 121 with 221 might have reversed the priority.

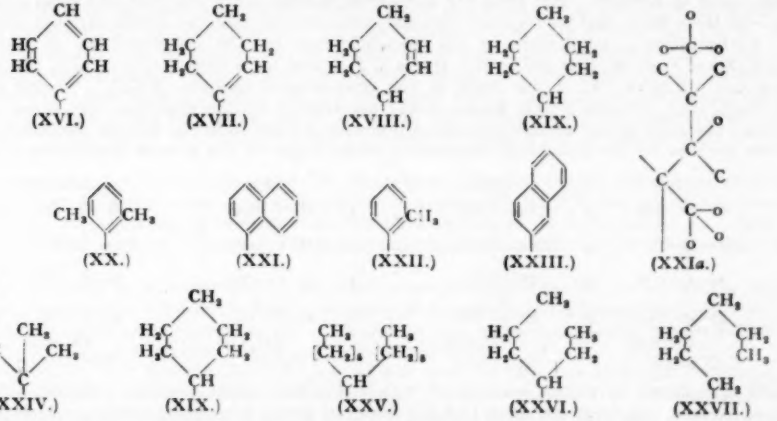
The method for selection of bond structures for aromatic rings has been arbitrarily made

the same as that for determining priorities by the general rule, solely in order to have only one method in use in the procedure as a whole. Some structures thus selected are illustrated in the



examples (VII)—(XV). The absence of any common chemical significance attaching to these particular structures is not considered a disadvantage. The structures are derived from the order of decreasing atomic number, and thus they as well as the rest of the sequence rule are divorced from such chemical theory as may change with the progress of science; it has been a main object to place the sequence rule on a non-ephemeral physical basis.

The priorities assigned by the rule to cyclic structures may be illustrated by selected examples. The order (XVI)—(XIX) is clearly as shown. So also is the order (XX)—(XXIII), followed by (XVI), etc., the ring junctions of α-naphthyl (XXI) being represented as in (XXI*a*). *cyclo*Hexyl (XIX) precedes *n*-hexyl (XXVII), the decision being taken already at the first carbon atom; *cyclo*hexyl also precedes 1-*n*-hexyl-*n*-heptyl (XXV) and longer radicals, the decision being taken at the " seventh " carbon atom which in *cyclo*hexyl is the original point of entry into the ring where the " chain " branches; for an " opened ring " such as (XXVI)



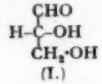
the decision is reached at an earlier stage; *tert.*-butyl, however, precedes *cyclo*hexyl; the complete priority order of these Groups is as given in the row of formulæ. In all these examples also the absence of a chemical logic is noticeable, and again no apology is made for this.

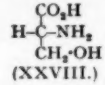
Other features of the sequence rule are, it is hoped, self-explanatory.

Examples of the sequence rule.

Nomenclature.—The symbols D and L chosen for use with the sequence rule should invariably be preceded by the numeral or letter used to designate the appropriate asymmetric atom; this symbol should be attached to the name of a substituent present on the asymmetric atom or, if no such substituent is named, to that part of the name which embraces the asymmetric atom in question. Examples are αL-alanine, βD-amino-αL-hydroxybutyric acid, 4D-hydroxy-2D-proline, and 9D : 10D-α-decalone. The attached positional numeral or letter supplies differentiation from previous uses of the letters D and L.

Brewster, Hughes, Ingold, and Rao (*Nature*, 1950, **166**, 178) have rigidly completed the genetic chain between D-glyceraldehyde (I) and D-serine (XXVIII); the sequence rule also


(I.)

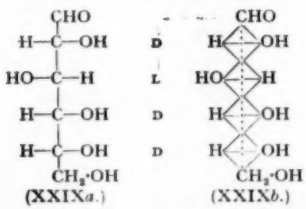

(XXVIII.)

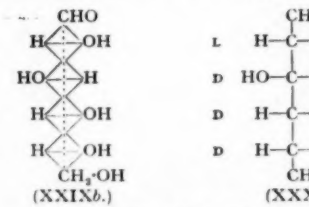
ascribes the D-configuration to (XXVIII), so that the prefix D deduced by the sequence rule and based on D-glyceraldehyde as "standard substance" corresponds also to the convention for serine. It is this correspondence, indeed, the large overall area of agreement between the proposed general notation and accepted sectional notations, that makes it advisable to use D and L to denote configurations deduced by the sequence rule (which was, in fact, framed so that it should yield a maximum of such agreement).

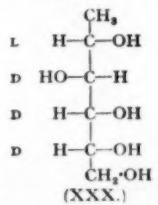
Thus the way is cleared for a rational nomenclature applicable both to carbohydrates and to amino-acids, without serious disturbance of existing conventions, and to a much wider field. The need for such a joint nomenclature follows from the fact that the prefix D, or more specifically D_g, for carbohydrates refers to the configuration at the highest-numbered asymmetric carbon atom, whereas the prefix D, or more specifically D_a, for amino-acids refers to the configuration at the α-carbon atom (corresponding to $C_{(2)}$ of an aldose sugar). Thus L_g-threonine is 2-amino-2 : 4-dideoxy-D_g-threonic acid. It will be shown below how such anomalies are overcome by use of the sequence rule.

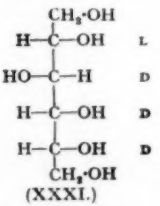
For hexoses, pentoses, and their derivatives the universally accepted trivial names define the stereochemistry of each asymmetric atom; α-D-glucofuranose, for instance, can be only one substance, and there is no need for further prefixes specifying the D- or L-configuration of carbon atoms 2—5. Similarly the universally accepted names for amino-acids need not be modified, except by the addition of the positional numeral or letter required for use with the sequence rule (as in αL-alanine). But there are unresolved nomenclature problems and some confusion in both these fields, and the sequence rule and nomenclature based on it offer rational solutions.

Carbohydrates.—Application of the sequence rule to the *aldehydo*-form of D-glucose (XXIX*a* = *b*) shows that the carbon atoms **2**, **3**, **4**, and **5** are respectively D, L, D, and D, *i.e.*, D-atoms all have OH to the right in the conventional formula (XXIX). Owing to the representation through which double bonds are treated by the sequence rule, these results remain the same in any semiacetal form of D-glucose, as well as in the derived glucosides. The same prefixes for the individual asymmetric atoms apply to the glucose derivatives in which

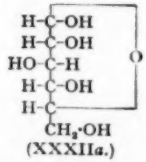

(XXIX*a*.)

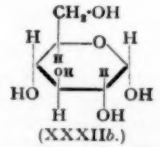

(XXIX*b*.)


(XXX.)


(XXXI.)

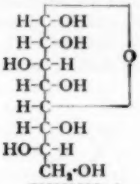
CHO is replaced by groups such as CN, CO_2H, $CO{\cdot}NH_2$, which precede $-CH(OH){\cdot}C$ by the sequence rule. If, however, as in (XXX), the CHO group is replaced by CH_3, which follows $-CH(OH){\cdot}C$ by the sequence rule, the configurations at $C_{(2)}$ and $C_{(3)}$ are reversed. It may be considered that the pentol (XXX) can barely be classed as a sugar derivative, but a similar

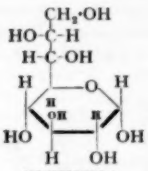

(XXXII*a*.)

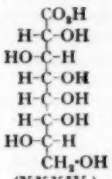

(XXXII*b*.)

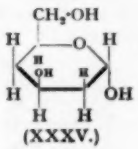
"reversal" is observed with D-sorbitol (XXXI). It is clear, therefore, that the relative positions of the H and OH in the conventional formulæ are no guide to the prefix to be attached to the separate atoms and that each case must be considered individually.

In α-D-glucopyranose (XXXII*a* = *b*) carbon atom number 1 has the L-configuration by the sequence rule; this substance might therefore be unambiguously named as 1L-D_g-glucopyranose or as 2L : 3D : 4L : 5D-tetrahydroxy-6D-hydroxymethylpyran, but there seems no need to disturb the generally accepted and simpler α-D-glucopyranose. Similar considerations apply to glycosides. L. F. Fieser (*J. Amer. Chem. Soc.*, **1950**, **72**, 623) has suggested that the configuration of individual atoms of pyranose and furanose sugars and their derivatives can be defined as α or β according to whether the hydrogen atom lies below or above the plane of the ring according to the conventional cyclic sugar formula. This convention is however restricted to cyclic carbohydrates and is thus less generally useful than the sequence rule.


(XXXIII*a*.)


(XXXIII*b*.)


(XXXIV.)


(XXXV.)

In the above and similar cases the present carbohydrate nomenclature is simpler than that which follows from the sequence rule, and need not be changed; but we shall next mention briefly three classes of compounds where the sequence rule can be usefully employed. There is not yet agreement on trivial names for sugars containing seven or more carbon atoms. A nomenclature based on the sequence rule is sufficiently exemplified by the names α-D-gluco-6D : 7L-octapyranose for (XXXIII*a* = *b*), and D-gluco-6D : 7L-octonic acid for (XXXIV); the α-D-gluco defines the configurations at positions 1—5, and those of the remaining asymmetric atoms are specifically added thereafter. In these names, it is at once evident that the 6D and 7L are derived by the sequence rule, since here the D and L are associated with positional numerals; and it should be clear that the D-gluco derives from the carbohydrate convention, because the D is attached to gluco and not associated with a position symbol: such names, involving mixed usage, are really abbreviations of, *e.g.*, α-D_4-gluco-6D : 7L-octapyranose, and the fuller names should be employed if the distinction in usage is not considered to be obvious otherwise.

Conversion of a CH(OH) group into CH_2 leaves open a choice of sugar names from which to derive that of the deoxy-sugar. According to the sequence rule, (XXXV) may be unambiguously termed 2L : 4L-dihydroxy-6L-hydroxymethyltetrahydropyran or, if it is desired to retain a sugar terminology, 2 : 4-dideoxy-1L : 3L : 5L-hexapyranose or perhaps 2 : 4-dideoxy-α-3L : 5L-hexapyranose.

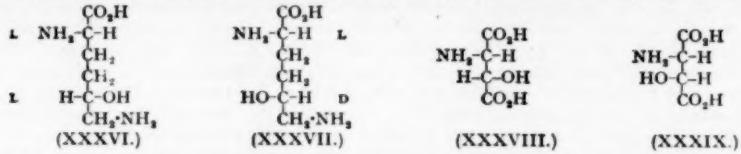
Current research on amino-sugars and amino-deoxy-sugars is leading to substances which can be considered as lying in the field of amino-acid chemistry, so that interpenetration of the D_g and D_s systems may become serious. The discussion of amino-acids which follows will show how the sequence rule can here too be used with advantage.

Amino-acids.—It has already been pointed out that the sequence rule and the standard convention accord the same configuration to serine; and the same is true for almost all the optically active amino-acids with only one (α-)asymmetric atom, for the order of priority will be NH_2, CO_2H, R, H for these substances.* It remains only to show how the sequence rule can be of benefit when more than one asymmetric atom is present, the previous conventions having led to difficulties in such cases. We shall use δ-hydroxylysine, β-hydroxyaspartic acid, 4-hydroxyproline, and threonine as examples.

The δ-hydroxylysine (XXXVI) has the L_s : D_g-configuration; we are concerned also with its diastereoisomeride (XXXVII) and the enantiomorphs of these two. According to the sequence rule, (XXXVI) has the L-configuration at the α- and at the δ-position and can

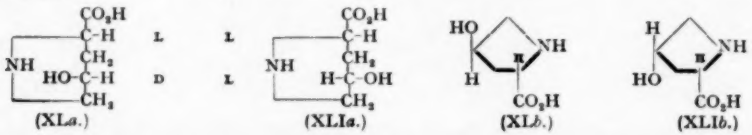
* The main exception known to us is cysteine (and, of course, cystine). The natural form, L_s-cysteine (inset), becomes aD-cysteine when named in accordance with the sequence rule. Such cases appear to be rare. In the literature of specialist fields, subscripts are often elided from the prefixes D_g, L_g, and D_s, L_s; but for cysteine, and in any other such examples, should they arise, it will be unwise either to drop the subscript when naming by a specialist convention, or, of course, to omit the position symbol when using the more general system here suggested.

accordingly be termed δL-hydroxy-αL-lysine. Its diastereoisomeride (XXXVII) can similarly be named δD-hydroxy-αL-lysine. The enantiomorphs become δD- and δL-hydroxy-αD-lysine.



(XXXVI.) (XXXVII.) (XXXVIII.) (XXXIX.)

The β-hydroxyaspartic acid (XXXVIII) can be semisystematically named α′L-hydroxy-αL-aspartic acid (or, quite systematically, αL-amino-α′L-hydroxysuccinic acid), and its diastereoisomeride (XXXIX) is then α′D-hydroxy-αL-aspartic acid. The necessity for special "trivial" prefixes, such as Dakin's para and anti (*J. Biol. Chem.*, **1921**, **48**, 273), is avoided by use of the general rule.



(XL*a*.) (XLI*a*.) (XL*b*.) (XLI*b*.)

Difficulty has attended attempts to reach internationally an agreed nomenclature for the diastereoisomerides (XL*a* = *b*) and (XLI*a* = *b*), which are often termed 4-hydroxy-L-proline and *allo*-4-hydroxy-L-proline, respectively. According to the sequence rule, (XL) has the L-configuration at position 2 and the D-configuration at position 4, and is accordingly named 4D-hydroxy-2L-proline. Similarly (XLI) is 4L-hydroxy-2L-proline. The enantiomorphs are 4L- and 4D-hydroxy-2D-proline respectively. The *allo*-prefix may thus be abandoned (cf. below); the new names are precise and short in these and all similar cases, and conform to a general rule.

It may be noted in further illustration of a previous remark, that in the conventional representation (XL*a*) the 4-hydroxyl group is on the left although the D-configuration attaches to this position. This contrasts with a novel suggestion (offered to the Subcommittee on Biochemical Nomenclature of the National Research Council, U.S.A.) which would name both the NH and the OH of (XL*a*) zephos (Z; west), and the OH in (XLI*a*) eos (E; east); such a convention would have quite limited applicability.

L_s-Threonine (XLII) and *allo*-L_s-threonine (XLIII) conform to the same pattern so far as the sequence rule is concerned. The former can be systematically named αL-amino-βD-hydroxybutyric acid or αL : βD-threonine, and the latter αL-amino-βL-hydroxybutyric acid or αL : βL-threonine. The names for the enantiomorphs are obvious. The names L-threonine and L-*allo*threonine, in which *allo* denotes the reversed configuration at the β-position, may not be willingly abandoned as they are rather generally used. Nevertheless, whereas the partial names gluco, ido, xylo, etc., used for carbohydrates, are quite satisfactory as they indicate precisely a definite steric relation of all the asymmetric atoms in each case, the prefix *allo* (meaning "the other") refers back to the configuration of the "normal" substance;* this

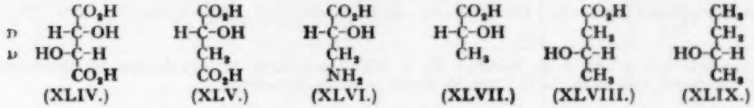
(XLII.) (XLIII.)

might have been satisfactory if *allo* were used only for one pair of substances, or if the asymmetric atoms of all the "normal" substances bore the same relation to one another; as it is, the prefix *allo* has no systematic significance, and the international difficulties mentioned above have centred mainly around constructing a generalisation as to which of a pair of diastereoisomerides is the normal substance. It seems more satisfactory to abandon the prefix *allo* as a means of stereochemical differentiation—if not for threonine, then certainly for other cases and for the more remote threonine derivatives.

Some Special Cases.—Tartaric acid, obviously on account of its historical importance, was

* If (XLII) is to be termed L_s-threonine, (XLIII) would have been more aptly named L_s-erythronine; but it seems to us preferable to place such names on a purely systematic basis.

chosen as a configurational standard by Fischer (*Ber.*, 1891, **24**, 2683). Freudenberg adopted the symbol D for the dextrorotatory acid (XLIV), and assigned as D-compounds the malic acid (XLV), the *iso*serine (XLVI), and the lactic acid (XLVII), which are genetically related to

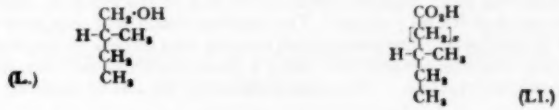


(XLIV.) (XLV.) (XLVI.) (XLVII.) (XLVIII.) (XLIX.)

D-tartaric acid ("Stereochemie," F. Deuticke, Leipzig, 1932, p. 575). However, dextrorotatory tartaric acid is L_g according to the rule that configurations under the carbohydrate system refer to the highest-numbered asymmetric atom (cf. Wolfrom in Gilman's "Organic Chemistry," Wiley, New York, 1943, p. 1545), although it is D_s under the rule that configurations by the amino-acid system refer to the α-carbon atom. The assignments accorded by the sequence rule are shown in (XLIV), and the acid is best named αD : α′D-tartaric acid. In this way Fischer's and Freudenberg's conventions are preserved. *meso*Tartaric acid might analogously be called αD : α′L-tartaric acid, though the *meso*-prefix does not need alteration. The configurational symbols assigned by the sequence rule to malic acid, *iso*serine, and lactic acid similarly agree with Freudenberg's symbols.

The prefix D or D_g customarily assigned to the lactic acid (XLVII) involves the special convention that it is formed from D-glyceraldehyde by the changes CHO ⟶ CO_2H and CH_2·OH ⟶ CH_3, rather than by CHO ⟶ CH_3 and CH_2·OH ⟶ CO_2H. Since the sequence rule also accords the D-configuration to (XLVII), the special conventions can be allowed to lapse, this being merely one example of the general rule.

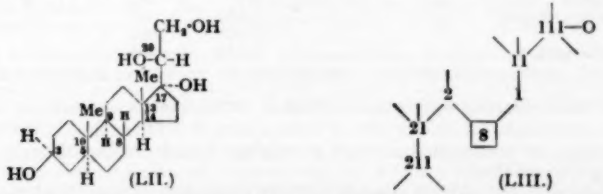
The dextrorotatory β-hydroxybutyric acid (XLVIII) and butan-2-ol (XLIX) have on occasions been assigned the L-configuration, although as Freudenberg points out (*op. cit.*, p. 679), there has been no justification for this. The sequence rule, however, accords the L-configuration to (XLVIII) and (XLIX), so that this assignment is now regularised by the general rule. Similar premature assignments can be similarly tested against the sequence rule as occasion arises.



(L.) (LI.)

Crombie and Harper (*J.*, 1950, 2685) have recently suggested that the dextrorotatory 2-methylbutanol (L) shall be considered as the parent of a series to be denoted by the prefix D_a, and has proposed rules by which derivatives, notably acids of the type (LI), may be correlated with it and included in the D_a-series. The sequence rule ascribes the D-configuration to (L), so that adoption of the rule would render the subscript "a" superfluous; acids (LI) also have the D-configuration by the sequence rule, as will most derivatives of (L), but in deciding this and similar cases it is essential that the sequence rule and not the rules of Crombie and Harper shall be applied.

Lastly, as a complex example, let us consider Reichstein's substance K on the (unproven) assumption that the orientation (LII) is correct in all its details. Determination of the priority of the Groups is simple except for position 8; there the analysis proceeds as in (LIII), where



(LII.) (LIII.)

bonds to carbon are indicated but bonds to hydrogen are omitted; the oxygen atom attached to atom 111 (position 17) determines the priority in the sense that the group staring with

$C_{(14)}$ precedes that starting with $C_{(8)}$. It transpires that, on the above assumption, the L-configuration is present at positions 3, 5, 9, 10, 13, and 14, and the D-configuration at positions 8, 17, and 20, and that accordingly Reichstein's substance K may be completely defined as 17-(1D : 2-dihydroxyethyl)-5L : 8D : 9L : 14L-perhydro-10L : 13L-dimethyl-*cyclo*pentanophenanthrene-3L : 17D-diol, or, more briefly, as *allo*pregnane-3L : 17D : 20D : 21-tetrol.

We are indebted to Drs. J. R. Johnson, W. T. Miller, and H. B. Vickery for helpful criticisms of a draft of this paper, and to Dr. L. C. Cross for many valuable discussions.

THE CHEMICAL SOCIETY, BURLINGTON HOUSE,
PICCADILLY, LONDON, W.1.
WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON, W.C.1

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NOTES.

132. *The Formation of Osazones. Part II. The Formation of Glucosazone.*

By G. J. BLOINK and K. H. PAUSACKER.

THE following work was undertaken in order to determine the effect of a number of compounds in catalysing the reaction between glucose and phenylhydrazine to form glucosazone.

Stempel (*J. Amer. Chem. Soc.*, 1934, **56**, 1352) has found that in an atmosphere of nitrogen glucose is not converted into the osazone in dilute mineral acid although, " contrary to general belief," glucose phenylhydrazone is formed. When he added an equivalent amount of acetic acid to the solution, the theoretical yield of osazone was rapidly obtained. We have verified Stempel's results but find that, in dilute mineral acid, the osazone is formed if the reaction vessel is filled with oxygen.

Accordingly, the catalytic effect of various other substances was investigated. Glucose (4·91 g.) was dissolved in an aqueous solution (15 ml.) of the catalyst, and phenylhydrazine (2·4 g.) in ethyl alcohol (15 ml.) added. The reaction vessel was stoppered after the air had been displaced by nitrogen. The precipitated osazone was filtered off at specified times. The pH of the solution was also determined (using a glass electrode) and was found to alter only very slightly during the reaction. The table summarises the results obtained.

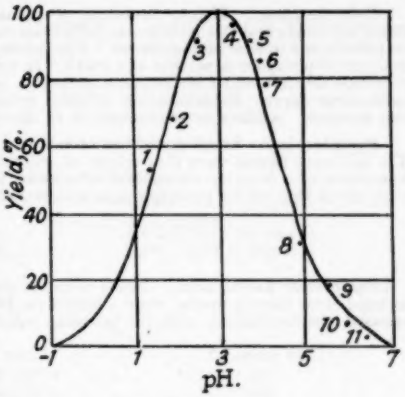
No. of expt.	Catalyst.	Normality.	Initial pH.	Yield, %. 4 days.	Yield, %. 3 weeks.
1	Oxalic acid	5·78	1·4	53	57
2	Citric acid–sodium phosphate buffer	—	1·90	68	—
3	Phosphoric acid	5·78	2·6	91	charred
4	Chloroacetic acid	5·78	3·2	98	100
5	Citric acid	5·78	3·8	91	100
6	Lactic acid	5·78	4·1	85	100
7	Acetic acid	5·78	4·2	79	99
8	,,	1·93	4·9	32	81
9	,,	0·64	5·4	19	48
10	,,	0·21	5·9	6	19
11	,,	0·075	6·3	3	—
	,, [a]	0·025	—	—	6
	Boric acid	5·78	6·4	3	charred
	Hydrochloric acid [b]	0·025	6·7	—	24
	,,	0·025	6·7	—	—
	Phthalic acid	0·025	6·9	—	3

[a] 15 Ml. of hydrochloric acid (0·075N.) were also added. [b] In an atmosphere of oxygen.

Zero yields were obtained when phenol (0·025 or 5·78N.), citric, succinic, or trichloroacetic acid (0·025N.), ammonium chloride (0·025N.), sodium acetate (0·025 or 5N.), piperidine (0·025N.), ammonia (0·025N.), or a saturated solution of sulphur dioxide, carbon dioxide, or hydrogen sulphide was used as catalyst.

It is thus seen that the yield of osazone is highly dependent on the pH of the solution, the maximum occurring at *ca.* pH 3. This is in contrast to the work of Garrard and Sherman (*J. Amer. Chem. Soc.*, 1918, **40**, 995), who claim that the optimum pH is 4·7.

The percentage yield of osazone (after 4 days) is approximately $100e^{-0.120(pH-2)^2}$, the theoretical curve and certain of the results (indicated by their experimental numbers given in the table) being shown in the figure. However, it may be noted that whenever high yields were obtained the catalysing acid was weak. When (as suggested by a Referee) sufficient hydrochloric acid was used to bring the pH to 3 the yield of osazone (after 4 days) was 4%. This result may be readily explained, for calculation, using the standard salt hydrolysis equations, shows that phenylhydrazine is almost completely converted by hydrochloric acid into the phenylhydrazinium ion whereas with 5·78N-acetic acid the conversion is *ca.* 90%. Conant and Bartlett (*J. Amer. Chem. Soc.*, 1932, **54**, 2881) have found that semicarbazone formation is acid-catalysed but proceeds *via* the free semicarbazide. If hydrazone formation, which is involved in osazone formation, follows the same mechanism, then the difference between hydrochloric and acetic acids at the same pH may be explained by their differing salt-forming capacities. Thus, though the above equation is applicable when weak acids are employed, it cannot be used for predicting the yield with strong acids.



CHEMISTRY DEPARTMENT, UNIVERSITY OF MELBOURNE,
VICTORIA, AUSTRALIA.

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133. *The Determination of Phosphorus in Deoxypentose Nucleic Acids.*

By A. S. JONES, W. A. LEE, and A. R. PEACOCKE.

SMALL amounts of organic phosphorus are frequently determined by Allen's method (*Biochem. J.*, 1940, **34**, 858) in which 60% perchloric acid is used for the conversion into orthophosphate in place of the sulphuric acid used by earlier workers (*e.g.*, Fiske and Subbarow, *J. Biol. Chem.*, 1925, **66**, 375). It has now been found that the latter reagent, with suitable additions, is more satisfactory for the determination of phosphorus in deoxypentose nucleic acids.

When perchloric acid was used for the digestion of these acids, the mixture required about 7 hours' heating to ensure release of all the phosphorus (see table; 2 ml. of nucleic acid solution were heated in micro-Kjeldahl flasks with 2·2 ml. of 60% perchloric acid, experiments being in triplicate). This long digestion time renders the method laborious and inaccurate and it is difficult to obtain consistent results with these substances.

Time of heating (mins.)	40	85	180	300	360	420	495
Phosphorus released (mg.)	0·027	0·032	0·037	0·045	0·046	0·046	0·046

A mixture of concentrated sulphuric acid, copper sulphate, potassium hydrogen sulphate, and a little powdered selenium had previously (Ma and Zuazaga, *Ind. Eng. Chem., Anal.*, 1942, **14**, 280) been found to release all the nitrogen from nucleic acids in about 2 hours. With such a mixture we find that phosphorus is completely released from deoxypentose nucleic acids in 45 minutes (subsequent to removal of water).

The procedure is as follows. To the solution (1—2 ml., containing 0·01—0·10 mg. of phosphorus), in a micro-Kjeldahl flask, concentrated sulphuric acid (0·3 ml.), a solution (0·5 ml.) containing copper sulphate (10 g./l.) and potassium hydrogen sulphate (120 g./l.), together with a few grains of selenium powder, are added. The water is removed by boiling and after a further 45—60 minutes' heating, the solution is allowed to cool and transferred to a 25-ml. flask. Thereafter, Allen's technique is employed,

the optical density being determined by means of a " Spekker'" absorptiometer (Ilford spectrum red filter No. 608).

The following experiments were carried out in order to validate the method.

Orthophosphates. Known amounts of potassium dihydrogen orthophosphate were treated as described above and the usual linear calibration curve of " Spekker " drum reading against the quantity of phosphorus present was obtained. The increase in drum reading for an increase of 0·01 mg. in the amount of phosphorus present was 0·046. It was necessary to heat the phosphate solution with the digestion mixture under conditions comparable with those of the determinations to obtain a consistent calibration curve. Determination of pure orthophosphate is therefore possible in the presence of this mixture. A blank determination on all the reagents was made.

Pyrophosphate. Small quantities of sodium pyrophosphate were treated as previously described. The following figures show that release of orthophosphate was quantitative within 1—2%. Therefore hydrolysis of a complex phosphorus compound will not stop at the pyrophosphate stage. However, only about 15% of the pyrophosphate was transformed into orthophosphate if heating was omitted.

P used as $Na_4P_2O_7$, mg.	0·020	0·040	0·060
P found as PO_4''', mg.	0·0198	0·0408	0·0608

Deoxypentose nucleic acids. Equal volumes of the same solution of a deoxypentose nucleic acid, isolated from herring sperm, were digested (in triplicate) for different times, and the orthophosphate released was determined, with the following results :

Time (mins.).*	Drum readings.	Mg. of P obtained as PO_4'''.
10	0·225, 0·224, 0·224	0·042
45	0·231, 0·229, 0·227	0·043
120	0·227, 0·227, 0·230	0·043

* After removal of water vapour, *i.e.*, after boiling for 10—20 minutes.

Heating for 45 minutes subsequent to removal of water was sufficient. The addition of 0·02 mg. of phosphorus, as orthophosphate, to the same amount of this same nucleic acid solution caused increases in the " Spekker " drum reading of 0·087, 0·090 and 0·093 in different experiments, the calibration curve predicting a value of 0·092. Hence within the limits of accuracy of the instrument, the determination of orthophosphate by this method is not vitiated by the presence of nucleic acid decomposition products.

The authors thank Professor M. Stacey, F.R.S. for his interest in this work and acknowledge gratefully receipt of a Beit Memorial Fellowship by one of them (A. S. J.).

DEPARTMENT OF CHEMISTRY, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM, 15.

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134. *The Vapour Pressure of Diphenyl, Dibenzyl, and Diphenylmethane.*

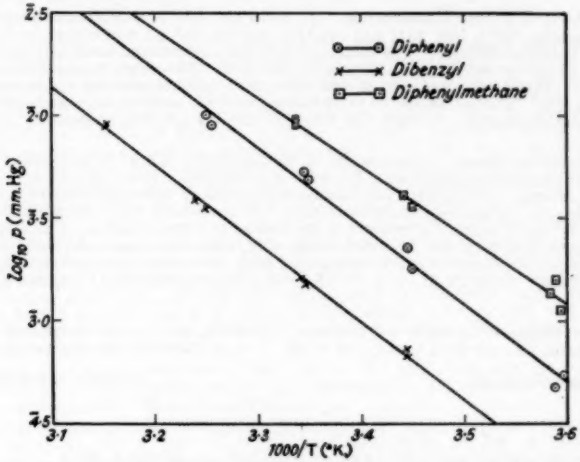
By NORMAN F. H. BRIGHT.

THE vapour pressures of diphenyl, dibenzyl, and diphenylmethane have been measured over the temperature range 5—45°, by the effusion method which was recently used for *cis*- and *trans*-azobenzene (Bright, Carson, and Dyson, *Research*, 1950, **3**, 185). This method is valid for pressures at which the mean free path of the molecules in the molecular beam is long in comparison with the dimensions of the effusion orifice. In the present work, this upper limit is of the order of $1—2 \times 10^{-2}$ mm. of mercury. The lower limit of applicability is fixed by the vacuum attainable in the evacuated space and by the convenience of experimental times involved; vapour pressures down to 10^{-5} mm. of mercury can be measured without great difficulty. In the present work, the lowest pressures encountered were well in excess of this limit.

Experimental.—The very pure hydrocarbons, provided by Miss M. F. Penney, of the Physical Chemistry Laboratory, Oxford, were characterised as follows : Diphenyl, m. p. 68·8—68·9° (Found : C, 93·3, 93·5; H, 6·6, 6·8. Calc. for $C_{12}H_{10}$: C, 93·5; H, 6·5%). Dibenzyl, m. p. 51·6—51·8° (Found : C, 92·3, 92·5; H, 7·8, 7·8. Calc. for $C_{14}H_{14}$: C, 92·25; H, 7·75%). Diphenylmethane, m. p. 25·0° (Found : C, 92·8, 93·0; H, 7·0, 6·8. Calc. for $C_{13}H_{12}$: C, 92·8; H, 7·2%).

The experimental results, shown in the figure, were treated by least square methods, to give equations of the form $\log_{10} p$ (mm. Hg.) $= -(A/T) + B$. Values of A and B, and the standard deviation of the determined vapour pressures, are given in the following table:

	Diphenyl.	Dibenzyl.	Diphenylmethane.
Temp. range	4·9—34·5°	17·1—44·2°	5·1—26·5°
A	3799	3783	3341
B	10·38	9·86	9·12
Standard deviation (%) of a determination of v. p.	±12·8	±4·8	±9·7



Discussion.—Previously published data for these hydrocarbons are confined largely to boiling points at higher pressure ranges (Garrick, *Trans. Faraday Soc.*, 1927, **23**, 561; Montillon, Rohrbach, and Badger, *Ind. Eng. Chem.*, 1931, **23**, 764). Our measurements, while not being in very good accord with the published data for the lower ranges, give quite good agreement for higher temperatures. Our values for latent heat are in reasonable accord with those obtained by Wolf and Weghofer (*Z. physikal. Chem.* 1938, *B*, **39**, 198). The comparatively low value for diphenylmethane is in accord with its surprisingly low melting point.

	Latent heat of sublimation (kcals./mol.).	
	Present work.	Wolf and Weghofer.
Diphenyl	17·4 ± 0·7	16·4 ± 0·2 at 22°
Dibenzyl	17·3 ± 0·3	17·5 ± 0·2 at 25°
Diphenylmethane	15·3 ± 0·7	17·2 ± 0·2 at 24°

IMPERIAL CHEMICAL INDUSTRIES LIMITED,
NOBEL DIVISION, RESEARCH DEPARTMENT,
STEVENSTON, AYRSHIRE.

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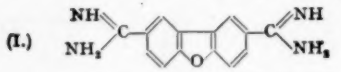
135. 3 : 6-*Diamidinodibenzofuran.*

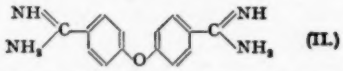
By J. S. MOFFATT.

3 : 6-DIAMIDINODIBENZOFURAN has been prepared because of its structural resemblance to di-(*p*-amidinophenyl) ether (phenamidine) (II) which is one of a series of aromatic diamidines prepared by Ashley, Barber, Ewins, Newbery, and Self (*J.*, 1942, 103) and shown to be active against *Trypanosoma rhodesiense* infections in mice (Lourie and Yorke, *Ann. Trop. Med. Parasit.*, 1939, **33**, 289). 3 : 6-Diamidinophenanthrene, a similar modification of di-4-amidinostilbene (stilbamidine), has been described by Barber and Stickings (*J.*, 1945, 167) as being only

slightly active as a trypanocide. The dibenzofuran derivative (I) was examined by Professor C. H. Browning, F.R.S., in the Bacteriology Department of this University. Administered



(I.)



(II.)

subcutaneously in doses approaching the maximum tolerated, it cured infections of *T. congolense* and *T. brucei* in mice.

Experimental.—**3 : 6-*Dicyanodibenzofuran.*** A mixture of 3 : 6-dibromodibenzofuran (5·5 g.) (Hoffmeister, *Annalen*, 1871, **159**, 215) and cuprous cyanide (6·5 g.) was added, in small portions, to boiling, purified quinoline (20 c.c.). The mixture was boiled under reflux for 30 minutes, allowed to cool, and then added to concentrated hydrochloric acid (200 c.c.). The mixture was boiled for a short time and then filtered. The residue was washed with dilute hydrochloric acid and water, and then sublimed at 220—230°/0·5 mm. The sublimate, on recrystallisation from acetic acid, gave needles (2·9 g.), m. p. 299°, of the *dicyanide* (Found : C, 76·9; H, 2·8; N, 12·8. $C_{14}H_6ON_2$ requires C, 77·1; H, 2·8; N, 12·8%).

3 : 6-*Diamidinodibenzofuran.* A suspension of the dicyanide (2·8 g.) in anhydrous ethanol (45 c.c.) was cooled at 0° and then saturated with dry hydrogen chloride. After 14 days at room temperature the mixture was filtered. The residue was washed with absolute ether and then kept for several hours in a vacuum desiccator containing sodium hydroxide. It was heated with saturated ethanolic ammonia (45 c.c.) at 45—50° for 6 hours. The mixture was cooled and then filtered. The residue (3·6 g.) was separated, by extraction with hot 2N-hydrochloric acid, into unchanged dicyanide (0·9 g.), and the *diamidine dihydrochloride dihydrate* which crystallised from 2N-hydrochloric acid in long needles (2·8 g.), m. p. >320° (Found : C, 46·7; H, 4·9; N, 15·2. $C_{14}H_{18}ON_4.2HCl,2H_2O$ requires C, 46·5; H, 5·0; N, 15·5%).

Grateful acknowledgment is made to Professor J. W. Cook, F.R.S., for his interest in this work, to the Medical Research Council for a Grant, and to Mr. J. M. L. Cameron for micro-analyses.

UNIVERSITY OF GLASGOW. [*Received, November 14th*, 1950.]

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136. *Difficulties in the Alkylation of* 2 : 6-*Di-iodo*-4-*nitrophenol.*

By J. H. WILKINSON.

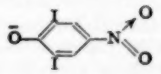
2 : 6-DI-IODO-4-NITROPHENOL cannot be alkylated in the conditions normal for the alkylation of phenols. Kalb, Schweizer, Zellner, and Barthold (*Ber.*, 1926, **59**, 1869), however, succeeded in preparing 2 : 6-di-iodo-4-nitroanisole by using a large excess of hot methyl sulphate and sodium hydroxide, and suggested that the difficulty was due to steric hindrance. That this cannot be the complete explanation is shown by the fact that several other 2 : 6-di-iodophenols have been alkylated in reasonably good yields under much milder conditions. Wheeler and Liddle (*Amer. Chem. J.*, 1910, **42**, 441) have described the methylation of 4-hydroxy-3 : 5-di-iodobenzoic acid with methyl iodide and alkali in methanolic solution (method I), and 3 : 5-di-iodoanisaldehyde dimethyl acetal was obtained in 50% yield by treatment of the hydroxy-aldehyde with methyl sulphate and alkali in methanol, initially at 0° (method II) (Wilkinson, *J.*, 1949, 2370). During the course of work on thyroxine analogues, it became necessary to alkylate a number of 2 : 6-di-iodophenols, and some of the results are shown in the accompanying table.

Phenol.	Alkylating agent.	Method.	Yield of product.
2 : 6-Di-iodo-*p*-cresol	Me_2SO_4	II	63%
4-Hydroxy-3 : 5-di-iodobenzaldehyde	Et_2SO_4	II	60%
p-Hydroxybenzaldehyde	Et_2SO_4	II	73%
2 : 6-Di-iodo-4-nitrophenol	Me_2SO_4	II	0—5%
p-Nitrophenol	Me_2SO_4	II	27%
Phenol	Me_2SO_4	II	70%
4-Hydroxy-3 : 5-di-iodobenzonitrile	EtI	I	60%

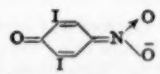
Iodine substitution in the *ortho*-position produces only a slight falling off in yield, whilst a nitro-group in the *para*-position to the hydroxyl group causes a marked reduction. When the two effects are combined, the yield by method II falls practically to zero. It is therefore concluded that the effect of the nitro-group on the ratio of the resonance forms (I and II) of the ion is the dominating factor, and that the iodine atoms may either enhance this or exert slight steric hindrance. The contribution of the normal phenoxide ion (I) is diminished to such an extent

that alkylation is negligible under mild conditions, whilst the ion (II) becomes the major component.

It is relevant to this explanation that a quinonoid substance is produced when 2 : 4 : 6-triiodophenol is oxidised under very mild conditions (cf. Woollett, Davis, Jones, and Neill, *J. Amer. Chem. Soc.*, 1937, **59**, 861). Also the intense orange colour of the sodium salt of 2 : 6-di-iodo-4-nitrophenol suggests the presence of (II).



(I.)



(II.)

Experimental (m. p.s are uncorrected).—*Method I.* 4-*Ethoxy*-3 : 5-*di-iodobenzonitrile.* 4-Hydroxy-3 : 5-di-iodobenzonitrile (von Auwers and Reis, *Ber.*, 1896, **29**, 2359) (9·3 g.) was dissolved in ethanol (100 c.c.), aqueous sodium hydroxide (40%; 5 c.c.) and ethyl iodide (15·6 g.) were added, and the mixture was heated under reflux for 2 hours. After evaporation to *ca.* 30 c.c., the mixture was filtered and cooled; 4-*ethoxy*-3 : 5-*di-iodobenzonitrile* (6·0 g., 60%) was precipitated. Recrystallisation from alcohol gave large needles, m. p. 110—111° (Found : I, 64·4. $C_9H_7ONI_2$ requires I, 63·8%). When heated under reflux with alcohol (3 c.c.) and 5N-sodium hydroxide (5 c.c.) for 1 hour, the nitrile (0·5 g.) was hydrolysed to 4-*ethoxy*-3 : 5-*di-iodobenzoic acid* (0·42 g.) which was obtained by pouring the mixture into water (50 c.c.) and acidifying it with acetic acid. The acid crystallised from 60% alcohol in needles, m. p. 208—209° (Found : C, 25·9; H, 2·2; I, 60·9. $C_9H_8O_3I_2$ requires C, 25·8; H, 1·9; I, 60·8%).

Method II. The phenol (0·1 g.-mol.) was dissolved in methanol (100 c.c.) and treated with methyl sulphate (0·1 g.-mol.). The mixture was cooled to 0—10° and treated with 40% sodium hydroxide (10 c.c.). In each case the temperature rose to *ca.* 70°. The mixture was set aside for 30 minutes, made alkaline (phenolphthalein), and diluted with water (500 c.c.). The product was collected either by filtration or extraction with ether. Ethylations were carried out similarly, except that ethanol (100 c.c.), ethyl sulphate (0·3 g.-mol.), and 40% sodium hydroxide (30 c.c.) were used, and the mixture was gently boiled for 10 minutes before being cooled and diluted with water. The following were among the alkyl phenyl ethers prepared by this method :

3 : 5-*Di-iodo*-4-*methoxytoluene* distilled at 106—108° at 10^{-4} mm., and was obtained as an almost colourless oil, which on cooling crystallised in waxy needles, m. p. 25° (Found : C, 26·5; H, 2·15; I, 67·5. $C_8H_8OI_2$ requires C, 25·7; H, 2·15; I, 67·8%).

4-*Ethoxy*-3 : 5-*di-iodobenzaldehyde* crystallised from light petroleum (b. p. 40—60°) in needles, m. p. 84° (Found : C, 27·0; H, 2·2; I, 63·0. $C_9H_8O_2I_2$ requires C, 26·9; H, 2·0; I, 63·2%). The *oxime* formed needles, m. p. 155°, from benzene (Found : C, 26·2; H, 2·15; N, 3·4. $C_9H_9O_2NI_2$ requires C, 25·9; H, 2·15; N, 3·4%). The aldehyde (1 g.) was heated under reflux with 1% methanolic hydrochloric acid (7 c.c.) for 1 hour and cooled, and the solution poured into excess of sodium carbonate solution and ice, giving the *dimethyl acetal* (1·03 g.), which crystallised from light petroleum (b. p. 40—60°) in needles, m. p. 47—48° (Found : C, 29·5; H, 3·1. $C_{11}H_{14}O_3I_2$ requires C, 29·5; H, 3·1%).

The microanalyses were by Drs. Weiler and Strauss, Oxford.

Department of Chemical Pathology,
Westminster Medical School (University of London),
London, S.W.1.

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OBITUARY NOTICES.

CHARLES STANLEY GIBSON.*

1884—1950.

CHARLES STANLEY GIBSON was born in Manchester on the 8th February, 1884. He was a member of a large family being the seventh son of his father, Joshua Gibson. He received his early education at the Manchester Grammar School, which he attended from 1897 to 1902. The educational standard of this school then, as now, was very high and it was one of the earliest schools to give an adequate training in science. After passing through the Modern Fifth he transferred to the science side where he came under the influence of Francis Jones. Francis Jones was probably one of the greatest of school chemistry masters; as a student at Owens College under Sir Henry Roscoe he, with Sir Edward Thorpe, assisted in the classical vanadium investigations and he never lost his interest in research. His lectures to the boys—and they were lectures rather than lessons—were profusely illustrated by experiments, in fact of such a high quality were these lectures that Gibson later found Professor H. B. Baker's lectures at Oxford to be largely a repetition of them. It was, however, the training in the laboratory which was particularly valuable. Each boy had his own set of apparatus and prepared all the simple gases and was then given a course of qualitative analysis. This followed the well-known Bunsen course of dry tests with the blow-pipe and borax beads. It was here that Gibson began to acquire the experimental skill which he was later to apply with such success.

In 1902 he proceeded to Corpus Christi College, Oxford, with a Natural Science Scholarship. It took him some time to settle down to life in an Oxford college, so different from his previous home life. He owed much to the advice and encouragement which he received from his tutor, F. C. S. Schiller, of whom he always spoke with respect and affection. His chemistry tutor was John Watts, who undoubtedly did much to make him the good organic chemist which he later became. Whilst at Oxford he had apparently few outside interests. It was a disappointment to him that when he graduated in 1906 he only obtained a second-class. He attributed this in part to his colour blindness and his inability to use a spectroscope in the practical examination. In spite of his defective eyesight he trained himself to be a most accurate observer with the polarimeter.

After graduation he joined Professor W. J. (later Sir William) Pope at the Municipal College of Technology in Manchester as a research assistant. Pope was then at the height of his powers, and this appointment was to influence the whole of Gibson's future life. Between these two men, so very different in physique and character, a close and intimate friendship developed. It is doubtful if, during Pope's lifetime, Gibson ever made any important decision without first consulting him.

To this laboratory (Manchester) towards the end of 1907 came John Read, who had recently taken his Ph.D. degree under Werner at Zurich; besides Gibson, the other research workers in Pope's private laboratory at that time were S. J. Peachey and George Jerusalem, a young chemist and crystallographer from Vienna. When Pope assumed the Cambridge chair in the autumn of 1908, Read and Jerusalem accompanied him. Later, in 1909, Gibson also migrated to Cambridge to work with Pope as the holder of a Senior Studentship of the Goldsmiths' Company. He undertook demonstrating work in the University Chemical Laboratory, and also gave a certain number of lectures to advanced students. At Manchester he had worked on organic compounds of gold. At Cambridge he devoted much time and effort—for he was an assiduous worker—to the synthesis and optical resolution of asymmetric phosphonium compounds; this tedius and often unpleasant work led to no satisfying result.

Gibson took the M.A. degree of Cambridge by incorporation, and became a member of Sidney Sussex College, of which Pope was a Fellow; here he undertook supervisory work in chemistry. During this period at Cambridge, Gibson's chief recreations were tennis and cycling. In the company of Read, and sometimes also of Jerusalem, he explored the countryside around Cambridge in the course of many pleasant cycling runs during fine week-ends. In the early summer of 1912 he went with Read on a tour of the West Country, starting at Bruton and ending at Porlock Weir; this he enjoyed greatly, in spite of his companion's puzzling dialect conversations with the natives, which struck strangely on his Northern ear. During this period

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he also paid his first visits to the continent, on two occasions with Dr. M. P. Applebey. He showed a keen appreciation of the continental ways of life and manners.

In his room at Cambridge, Gibson exercised his skill as a pianist and sometimes held modest musical gatherings. Together with Read, he became a frequent visitor at Pope's house in Brooklands Avenue, where upon rare occasions Pope might be induced to play the violin. Gibson also brought together a number of research men from the University Chemical Laboratory in a so-called Alembic Club. At meetings held in the rooms of the various members—among whom were Read, Jerusalem, John Thomas, and John Weir—papers on research subjects of current interest were given and discussed by the members. Gibson took a great interest in this Club, which fulfilled a very useful function during its existence of several sessions.

In 1912 he was appointed to the Chair of Chemistry in the Maharajah's College at Trivandrum, an affiliated College of the University of Madras. Although Gibson's predecessor, Dr. A. W. Bishop, had been a student of Claisen and W. H. Perkin, jun., he had done little to improve the teaching facilities which were very primitive. To this college Gibson brought new life. Undeterred by the difficulties and having re-organised the courses of instruction he immediately embarked upon original research. He succeeded in persuading the Travancore Government to supply him with a fine spectro-polarimeter but preparative work was almost impossible. Fortunately I was able to arrange for him to pay frequent visits to Madras to give courses of University lectures during which time he could work in my laboratory under conditions which, although poor, were somewhat better. We were thus able to renew a school friendship but collaboration at this time did not last long. Gibson was intensely patriotic and on the outbreak of the war in 1914 he felt he must return to England. Not being a British Government servant he was able in 1914 to get seconded for War Service and he did not return to India.

In England he immediately rejoined Pope and their work on the manufacture of mustard gas is too well known to require a detailed discussion. Unfortunately during the course of this work, owing to an accident in a works, Gibson suffered from gas poisoning and there is little doubt that he never fully recovered from this. His services to the country were recognised in 1919 by the award of the O.B.E. and during the same year he was appointed Professor of Chemistry at the Egyptian Government School of Medicine in Cairo. His stay there was, however, to be very brief and on the transfer of the late Professor T. M. Lowry to Cambridge he succeeded him in 1920 at Guy's Hospital Medical School. Here he was to remain until September 1949, when he became Emeritus. He took his teaching duties very seriously and devoted much attention to the preparation of his lectures and to the practical courses of his medical and dental students. Evidence of this is to be found in his publications, and by his membership of the Board of Studies he did much to improve the standards of the teaching of chemistry in the London Medical Schools. Whilst greatly appreciating the work which he was doing, he was disappointed never to have had the opportunity of training advanced students and building up a school of research.

His duties in the medical school did not exhaust his energies and he gradually became involved in the work of scientific societies. In company with Pope he attended many international meetings and he greatly enjoyed his continental visits. His major interest for many years was, however, the Chemical Society, and in 1924 he was appointed one of the Honorary Secretaries, a post which he continued to hold until 1933. These were years of great difficulty and as the Senior Secretary he shouldered most of the burden. It was during this period I enjoyed for a time the hospitality of his laboratory and I saw how heavy the burden was and how seriously he took his duties. After ceasing to be secretary he was Vice-President for two periods, 1933—1936 and 1942—1945, whilst he was for many years a member of the Publication Committee. His loyalty to the Society was shown once again in 1945 when on the sudden death of the editor, Dr. Clarence Smith, he undertook the onerous editorial duties until a successor could be found. His long connection with the Chemical Society resulted in close friendships with Emile Mond and A. J. Greenaway and for a number of years his holidays both at home and abroad were spent with them. From his friendship with Greenaway arose his interest in organic nomenclature. He was for many years a British representative on the Organic Chemistry Nomenclature Commission of the International Union. Although his health was already very precarious he attended meetings of the Commission in Amsterdam in September 1949.

On the formation in 1935 of the Academic Assistance Council (later the Society for the Protection of Science) he was with Sir William (later Lord) Beveridge appointed as Secretary.

No better choice could have been made. He possessed just the right abilities of tact and sympathy required for carrying out what, in many cases, were somewhat distasteful duties. He was interested also in the British Association, being the Recorder of Section B from 1927 to 1931 and President of the Section at the Cambridge meeting in 1938. He also served on the Councils of the Royal Institute of Chemistry and of the Royal Society of Arts.

At the outbreak of war in 1939 Gibson at once placed his services at the disposal of the Government. For a time he worked at the Board of Trade but he did not find the work congenial nor of a kind to offer sufficient scope for his qualifications. Later he became the Senior Gas Adviser for the London Region and subsequently for Region 12. Undeterred by the difficulties involved in the removal of the Medical School to Tunbridge Wells he carried out his duties most energetically. He organised an excellent course of lectures for gas identification officers and he himself conducted anti-gas practical classes. At the same time he vigorously carried out his research on gold films and it was an intense disappointment to him that the anti-glare glasses which he designed were found to be unsuitable for use in the R.A.F.

These very varied activities gradually affected his health and in 1947 he had a slight stroke, from which, however, he made a remarkable recovery. In 1949 he had a second, severe stroke, which was followed by pleurisy and pneumonia. He made a partial recovery and when I saw him last January he spoke with his usual optimism and courage of travelling to either Torquay or the South of France to recuperate. In spite of the devoted nursing of Mr. and Mrs. Nield, who had looked after him for more than 20 years, he gradually failed and died on the 24th March.

Gibson was not married and when he first settled in London, he lived in St. Thomas Street near the hospital with Professor T. B. Johnstone. In 1930 he built a house at Kingswood, Surrey, laying out a garden from which he derived much pleasure. He had many interests besides chemistry. In his younger days he was an accomplished pianist but he was always critical of his own performance and latterly satisfied his love of music by listening to the B.B.C. concerts. He had a large collection of pestles and mortars and from his friend, A. J. Greenaway, he inherited a number of Kate Greenaway's paintings. His physique did not enable him to become a very active participant in games, but he was a good swimmer.

His services to science did not pass unrecognised. As already mentioned he received the O.B.E. in 1919 and was elected to the Fellowship of the Royal Society in 1931. He was an honorary member of the Société de Chimie Industrielle.

Scientific work.

Gibson's output of original work was very considerable and he was the author of about 120 memoirs and a number of books. This output was the more remarkable since, except for a few years whilst he was a member of the Gas Warfare Board, he had no paid assistant and the majority of his collaborators were members of the teaching staff. Apart from a few minor papers, his researches were limited to four main fields—stereochemistry, organic arsenic compounds, natural products, and organic compounds of gold. It was in the last-mentioned field that he made his most important contributions to science.

Stereochemistry.—Through his close association with Pope, Gibson naturally developed a leading interest in stereochemistry. He carried out much excellent and painstaking work in this field over a long period, the results of which were published chiefly in our *Journal*. Already during his first period at Cambridge (1909—1912) he devoted much of his time and energy to work on the preparation of quaternary phosphonium salts of the type $PR_1R_2R_3R_4X$, starting from monosubstituted chlorides, $RPCl_2$, and endeavouring to introduce other radicals by means of such reagents as mercury diaryls and Grignard reagents. It was hoped that a suitable halide salt of this type, when treated with the silver salt of one of the optically active camphor acids, would prove capable of optical resolution, after the pattern of Pope and Peachey's allylbenzylmethylphenylammonium iodide. Gibson found, however, that the synthesis of mixed phosphonium salts of the required type presented great difficulties, and in spite of repeated attempts he was unable to obtain a satisfactory product.

The bulk of Gibson's stereochemical work was concerned with optical resolutions of externally compensated acids and bases of various kinds. In 1910 (with W. J. Pope, *J.*, **97**, 2207), in studying the resolution of pavine with (+)-α-bromocamphor-π-sulphonic acid, he found that, conversely, the (±)-acid was also readily resolved by pavine, the (+)-base leading to the (−)-acid through the less soluble diastereoisomer, (+)-B, (−)-A. At this time also (with W. J. Pope, *ibid.*, p. 2211) he made accurate measurements of the rotatory powers of (+)-camphor-10-sulphonic acid and some of its inorganic salts.

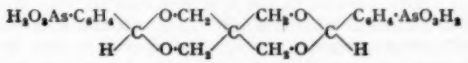
Considerably later (with H. Burgess, *J. Soc. Chem. Ind.*, 1925, **44**, 496T) he devised what is probably still the best way [unless a supply of (−)-camphor is available] of gaining access to the (−)-form of this acid, so valuable for many stereochemical purposes. The (±)-acid, prepared by sulphonating synthetic camphor, is treated with brucine in such a way as to remove most of the (+)-acid in the form of the salt (+)-A, (−)-B; the impure (−)-acid obtained from the mother-liquors is then recrystallised about five times from ethyl acetate, until optically pure.

A particular interest in optically active forms of bases and amino-acids is exemplified in Gibson's optical resolution of benzoylalanine, using strychnine and brucine (with W. J. Pope, *J.*, 1912, **101**, 939); of (±)-*sec.*-butylamine, using the (+)-form of the π-acid (with W. J. Pope, *ibid.*, p. 1702); of (±)-toluene-*p*-sulphonylalanine, using strychnine and brucine (with J. L. Simonsen, *J.*, 1915, **107**, 799); of (±)-tetrahydro-β-naphthaquinaldine (-5 : 6-benzquinoline) (with J. L. Simonsen, *J.*, 1915, **107**, 1148); of naphthalene-α- and -β-sulphonylalanine (with W. M. Colles, *J.*, 1924, **125**, 2505); and of (±)-*p*- and (±)-*m*-nitrobenzoylalanine (with W. M. Colles, *J.*, 1928, 99; 1931, 270).

In collaboration with G. M. Bennett (*J.*, 1923, **123**, 1570), alone (*J.*, 1927, 342), and with J. H. Nutland and J. L. Simonsen (*J.*, 1928, 108), he published a series of investigations on the isomerism of reduced derivatives of quinoxaline.

Finally, a special interest attaches to his introduction in 1929 (with B. Levin, *J.*, 1929, 2754) of (+)-nor-ψ-ephedrine as a basic resolving agent. This airly strong base of low molecular weight has the structure, $HO{\cdot}CHPh{\cdot}CHMe{\cdot}NH_2$, and is readily obtainable from a Chinese drug, Ma Huang. Gibson used it (*loc. cit.*) for resolving (±)-benzenesulphonylalanine and (±)-*N*-phenylalanine-amide-4-arsinic acid, and also (with B. Levin, *J.*, 1929, p. 2759) (±)-*N*-2-methylphenylalanine-amide-4-arsinic acid.

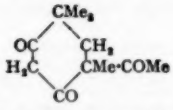
Later (with B. Levin, *Proc. Roy. Soc.*, 1933, *A*, **141**, 494) he provided the most striking example of the successful introduction of this resolving agent by the use of its (+)- and (−)-forms, achieving the resolution of an arsonic acid having molecular dissymmetry. The condensation of benzaldehyde-*p*-arsonic acid with pentaerythritol gave the tetrabasic (±)-*spiro*bis-3 : 5-dioxan-4 : 4′-di(phenyl-*p*-arsonic acid),

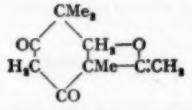


Tetrasodium salts of this acid were obtained, having in aqueous solution $[\alpha]_{5461}^{20}$ ±70·2°.

Naturai Products.—On taking up his Indian appointment Gibson continued for a time to work on stereochemical problems but he soon realised the importance of studying the natural products of the country. Our plans to collaborate in these investigations were abruptly terminated by the war and Gibson's departure to London. Only one short paper on the constituents of the bark of *Hymenodyciyon excelsum* was published (*J. Roy. Asiatic Soc., Bengal*, 1916, **12**, 161).

Later when I was afforded two periods of hospitality in his laboratory at Guy's Hospital we were able to resume our joint work, the results of which were published in eight papers communicated to the Chemical Society. Here reference need only be made to the publications on angustione and dehydroangustione (with A. R. Penfold and J. L. Simonsen, *J.*, 1931, 1184; with R. S. Cahn, A. R. Penfold, and J. L. Simonsen, *ibid.*, p. 286). In an earlier examination of the oil from *Backhousia angustifolia* Penfold had separated an oil with strong phenolic properties. A detailed examination of this material showed it to be a mixture of two optically active β-diketones, (I) and (II), the structures of which were conclusively established. At the

(I.) 

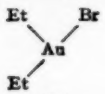
 (II.)

time only one other natural β-diketone, diosphenol, was known, but more recently Penfold and his collaborators have described a closely allied substance, leptospermone.

Organic Compounds of Arsenic.—Immediately after the war Gibson published (with W. J. Pope, *J.*, 1920, **117**, 271) the more scientific aspects of their work on di-2-chloroethyl sulphide and also on some related problems involving selenium compounds (with W. H. Bausor and W. J. Pope, *ibid.*, p. 1453; with H. C. Bell, *J.*, 1925, **127**, 1877). His membership of the Gas Warfare Committee resulted in his taking an interest in arsenic compounds and on this

subject, in collaboration more especially with Dr. (now Professor) H. Burton and Dr. J. D. A. Johnson, he published some 20 papers dealing with the chemistry of 10-chloro-5 : 10-dihydrophenarsazine. Although there were previous references in the literature to this substance, Gibson (with H. Burton, *J.*, 1926, 450) was the first to devise a convenient method for its preparation and also to report a synthesis which left no doubt as to its structure. Methods were devised also for the preparation of numerous derivatives containing alkyl, halogen, and nitro-groups, whilst many errors in the literature were corrected. A full résumé of this work was published (with J. D. A. Johnson and D. C. Vining, *Rec. Trav. chim.*, 1930, **49**, 106) in reply to certain criticisms which had been made on the structure assigned to phenarsazine. There can be little doubt that the experience gained in this difficult experimental work was of great value when Gibson returned to the study of the organic compounds of gold.

Organic Compounds of Gold.—Gibson's interest in the organic chemistry of gold was first aroused whilst he was working in collaboration with Pope (*J.*, 1907, **91**, 2061). With the comparatively recently described Grignard reagent, they examined the reaction of ethylmagnesium iodide on the ethereal solution of gold tribromide, being able to isolate diethylmonobromogold, but in poor yield. At the time little study was made of the chemistry of this first organogold derivative beyond noting that it formed a compound (II) with ammonia and reacted with bromine to give what was believed to be monoethyldibromogold, (III). Nor was it realised that (I) and (II) were dimeric.



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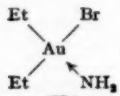
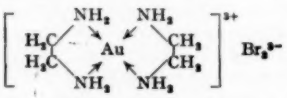


(II.)

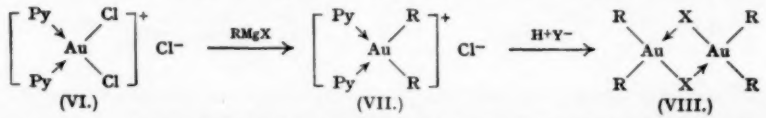
(III.)

Work in this field was not resumed until 1930 when (with J. L. Simonsen, *J.*, 1930, 2531) improved methods for preparing this compound were devised and a study of its properties and reactions was begun. To this field of research Gibson devoted the remaining years of his active career. The poor yields obtained in the first preparations were probably partly due to the insolubility of the gold halides in ether and in his early work Gibson spent much time in the search for more suitable starting materials. In the course of this several co-ordination compounds of gold halides with amines were isolated, notably bisethylenediaminogold tribromide (IV) and pyridinotribromogold (V; Py = C_5H_5N, X = Br), the latter an analogue of the

(IV.) 

(V.)

chloride (V; X = Cl) isolated by François in 1903. Although the addition of Grignard reagents to cold suspensions of pyridinotrichloro- and -tribromo-gold in ether, in which they are very slightly soluble, and in pyridine, in which they dissolve sparingly, gave little improvement in the amount of dialkyl derivatives isolated, the former compound was destined to be the chosen starting material for many of Gibson's preparative experiments. This compound dissolves in hot pyridine, as François had shown, to give dipyridinodichlorogold chloride (VI), which separates, on rapid cooling of the well-stirred solution, in the form of very small red needles. The addition of Grignard reagents to such a cold well-stirred suspension, together with improvements in the isolation of the products, resulted in yields of dialkylgold halides as high as 45%, calculated on the gold compound used. The course of the reaction is believed to be :

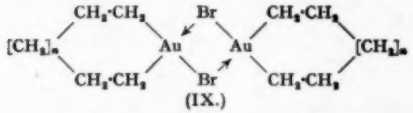


(VI.) (VII.) (VIII.)

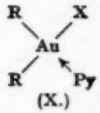
the first product being the dipyridinodialkylgold chloride (VII) which, having no halogen directly attached to the gold atom, is unable to react further with the Grignard reagent and is therefore " protected " by the pyridine. If the acid, HY, used in the liberation of (VIII) from (VII) is a halogen hydracid, the halogen X which appears in the dialkyl gold compound is found to be whichever is the more polarisable, or less electronegative, of X and Y. The

halogen-bridge constitution which was assigned by Gibson, after cryoscopic data had revealed that these compounds were dimeric, was subsequently confirmed in the case of diethylmonobromogold (VIII; R = X = Br) by an *X*-ray investigation by Hampson and Powell.

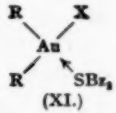
In addition to diethylmonobromogold, Gibson described dimethylmonoiodo-, di-*n*-propylmonobromo- and di-*n*-butylmonobromo-gold; and also *cyclo*pentamethylenemonobromo- (IX; $n = 1$) and *cyclo*decamethylenemonobromo-gold (IX; $n = 6$), both of which were formed by the action of the Grignard reagent prepared from pentamethylene dibromide, and both of which were markedly unstable.



(IX.)

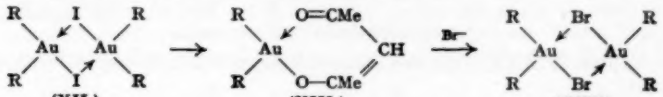


(X.)



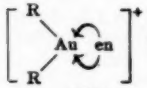
(XI.)

The halogen-bridged structure of the dialkylgold halides was shown to be split on treatment with many reagents, to give non-electrolytes or salts. Thus pyridine and dibenzyl sulphide yielded the non-ionic pyridino- (X) and (dibenzyl sulphide)-gold halide (XI), respectively; the ammonia derivatives, one example of which, (II), has already been noted, were of the same type. In consequence of the insolubility of the thallous halides, thallous acetylacetone reacted with (VIII) to give the corresponding dialkylgoldacetylacetones (XIII), which could be used as intermediates in the replacement of one halogen by another in a given dialkylgold halide since (XIII) was readily reconverted into (VIII) by the appropriate halide ion. As example of this may be instanced the conversion of the iodide, (XII) into the bromide (XIV), as follows:

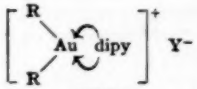


(XII.) (XIII.) (XIV.)

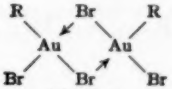
Ethylenediamine (en) caused fission of the halogen bridges, chelating with the gold atom with the formation of salts (XV; X = halogen) containing a complex gold cation. These were quite stable compounds and provided a very convenient means of storing the parent dialkylgold halides which could be liberated from them readily by acid. Di-2-pyridyl gave rise to salts (XVI), also containing a cation in which the diamine was chelated, but differing from (XV) in that no solid examples could be isolated in which the anion was halide, though evidence was obtained that such salts existed in aqueous solution. The nature of those examples of (XVI) which were obtained and of similar ethylenediamine compounds is discussed below.



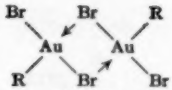
(XV.)



(XVI.)



(XVII*a*.)

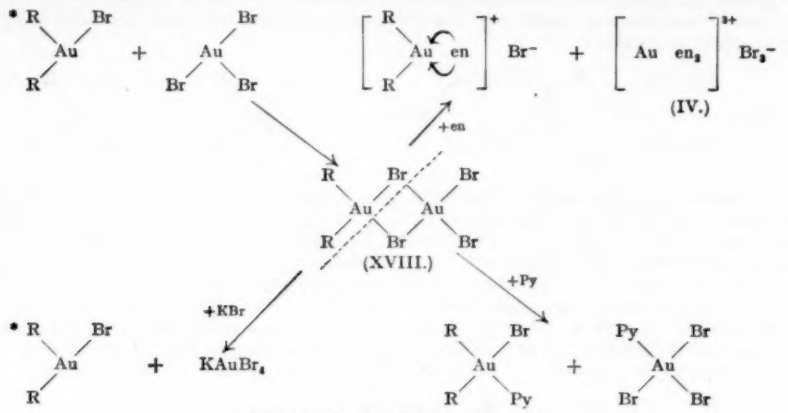


(XVII*b*.)

The reaction between diethylmonobromogold and two molecules of bromine, whereby monoethyldibromogold, (III), apparently resulted, proved on re-investigation to be general, and to give dimeric products. The manner in which these reacted with potassium bromide, pyridine, and ethylenediamine, together with their formation from the dialkylmonobromogolds and gold tribromide, outlined diagrammatically below, compelled Gibson to abandon his original belief that they were genuine dimeric monoalkyl derivatives, which should be able to exist in *cis*- and *trans*-forms (XVII*a* and *b*), and to formulate them as (XVIII). True monoalkylgold compounds have yet to be prepared.

By the interaction of dialkylgold halides with silver salts the halogen atoms were replaced by a variety of other groups. Diethyl- and di-*n*-propyl-monocyanogold, prepared in this manner, were non-electrolytes containing no less than four atoms of gold per molecule. These were assigned the constitution (XIX) in accordance with the accepted planar distribution of the valencies of four-covalent gold, and, in the case of the *n*-propyl compound, this was confirmed by an *X*-ray examination by Powell and Phillips. The but recently isolated diethylthiocyanatogold, on the other hand, was dimeric and for this the structure (XX) was preferred.

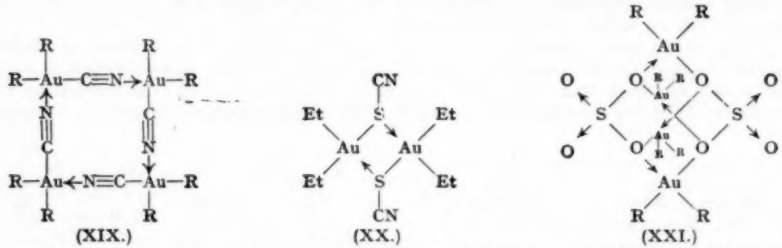
Silver sulphate and diethyl- and di-*n*-propyl-monobromogold yielded colourless crystalline compounds of peculiar properties. Though sparingly soluble in hydrocarbon solvents, they dissolved in ethanol and acetone, and the determination of the molecular weights in boiling acetone showed the ethyl derivative to contain four atoms of gold per molecule. No proof of the structures of these substances has yet been obtained but chemical and stereochemical



* Half molecules of (XIV) for clarity.

considerations point to (XXI) as the only reasonable way in which the required number of atoms could co-exist.

Unlike the halogeno-, cyano-, and thiocyanato-complexes, the sulphato-compounds were soluble in water. Their solutions gave an immediate reaction for sulphate ion and were presumed to contain the aquo-salts resulting from the disruption of the sulphate bridges by

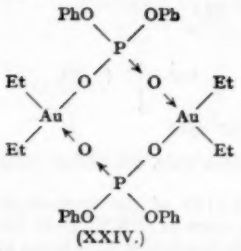


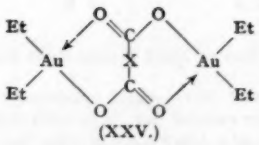
water, though no such salt has been isolated in the solid state. No other type of bridged complex has yet been found to behave in this way, indeed diethylthiocyanatogold (XX) was unaffected even by such powerful co-ordinating agents as ammonia, ethylenediamine, and di-2-pyridyl. Thiourea and thioacetamide alone of the reagents examined split the four-membered ring

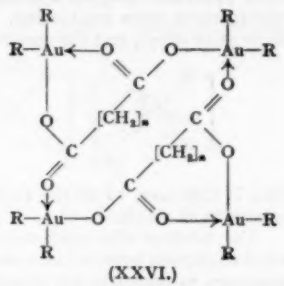
system to yield identifiable products, (XXII and XXIII). The halide and cyanide bridges appear to be of intermediate stability.

Non-electrolytes, exactly analogous in constitution to (XXI), resulted from the action on diethylmonobromogold of disilver phenyl phosphate and disilver phenyl arsonate, whilst silver diphenyl phosphate yielded the dimeric non-electrolyte (XXIV). Unlike (XXI), these are insoluble in water.

Interaction of the sulphato-complexes in aqueous solution with salts of dicarboxylic acids led to the isolation of non-electrolytes of various molecular complexities. The oxalato- (XXV; X = nil) and the phthalato-compound (XXV; X = *o*-$C_6H_4<$) each contained two atoms of gold per molecule. To the complexes derived from malonic up to suberic acid, containing

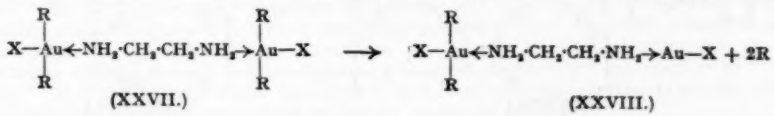

(XXIV.)


(XXV.)


(XXVI.)

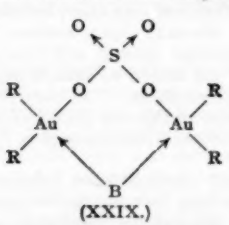
four atoms of gold per molecule, Gibson assigned provisionally the structure (XXVI; n = 1—6). The *iso*phthalate compound had no less than six gold atoms per molecule, whilst that derived from terephthalic acid was so insoluble that molecular-weight determinations were impossible, and extended linear polymerisation was postulated.

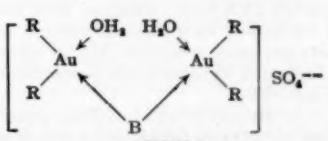
As had already been indicated, two molecular proportions of ethylenediamine convert dialkylgold halides into salts (XV; X = halogen). In the case of the cyanides no such salts could be isolated, the only products of the reaction being compounds, $(R_2AuCN)_2$en, in which it was believed that the diamine was " bridging " two R_2AuCN units, as in (XXVII; X = CN).


(XXVII.) (XXVIII.)

Gibson showed that under suitable conditions it was possible to prepare analogous compounds of dialkylgold halides and tetra-alkylsulphatodigolds (XXI), with ethylenediamine and di-2-pyridyl. Thus to the " bridged " sulphato-complexes the structure (XXIX; B = en or dipy) was given, their solubility in water to give sulphate ions being ascribed to the formation of aquo-salts (XXX), as in the case of the sulphato-complexes themselves.

The clue to the true constitution of these supposedly " bridged " compounds came as a result of a study of the dealkylation reactions which they underwent when heated. As early as 1935 Gibson recorded that ethylenediaminotetra-*n*-propyldibromodigold (XXVII; R = Pr^n,

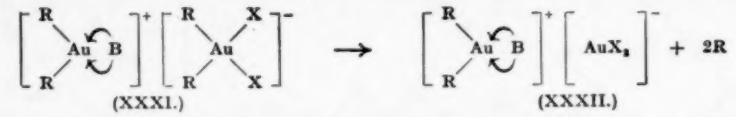

(XXIX.)


(XXX.)

X = Br as then formulated) lost only *half* its alkyl groups when heated in chloroform solution, to give a substance which he believed to be (XXVIII; R = Pr^n, X = Br). At the time no comment was made on the fact that whereas in the solid state dealkylation of (XXVII; R = Pr^n, X = Br) set in with uncontrollable vigour below 100°, (XXVIII; R = Pr^n, X = Br), though so closely related, lost its alkyl groups only at temperatures approaching 140°. Later in 1935 was published an account of the parallel reactions of monoethylenediaminotetraethyl- and tetra-*n*-propyl-dicyanodigold [believed to be (XXVII; X = CN, R = Et or Pr^n)], the products of the semidealkylation of which were recognised to be salts and correctly formulated

as aurocyanides (XXXII; X = CN, R = Et or Pr^n, B = en). These so similar reactions were, however, not correlated at the time.

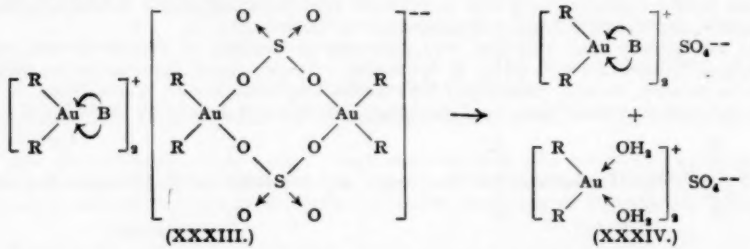
Further investigation of ethylenediamine- and dipyridyl-bridged halides and cyanides, not only of type (XXVIII) but also of type (XXVII), showed that in dilute solution in nitrobenzene their molecular weights approached half their formula weights and that their solutions in nitrobenzene were conducting. These were hence re-formulated as (XXXI) and (XXXII) B = en or dipy), and the semidealkylation reaction was represented by :



(XXXI.) (XXXII.)

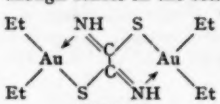
This is thus seen to be the entire loss of alkyl groups from the *anion only*, the cation being known to be stable.

The bridged ethylenediamine and di-2-pyridyl compounds (XXIX) of the tetra-alkyl-sulphatodigolds behaved in a similar manner but, in re-formulating them as (XXXIII), it was necessary to postulate the presence of a dimeric anion since the salts in solution were found to give rise to three ions. The effect on them of dissolution in water, as a result of which sulphate ion is disengaged, is hence represented by :



(XXXIII.) (XXXIV.)

As a result of these investigations much information accumulated regarding the stability of heterocyclic ring systems containing gold, and to augment this still further the reactions of diethylmonobromogold with 2-aminoethanethiol and dithio-oxamide were studied. Whilst the latter yields a stable complex (XXXV), the complex (XXXVI) derived from the former, though stable in the solid state, underwent in benzene and bromoform solution a rapid change which was attributed, at least in part, to inherent instability of the five-membered ring. The stability of (XXXV) was ascribed to resonance in the five-membered rings. The compound (XXXVI) gave also a sulphilimine (XXXVII) and reacted with ethyl bromide to give an oil for which, in spite of its physical characteristics, the ionic structure (XXVIII) was most favoured since it could be converted into a picrate (XXXIX), identical with that obtained by the action of sodium picrate on a solution containing diethylmonobromgold and 2-aminoethyl sulphide. The possibility of an alternative non-ionic structure (XL), or an equilibrium mixture of this and (XXXVIII), similar to that suggested to explain the properties of the *NN*-diethylenediamine complex (XLI), was thought less likely.

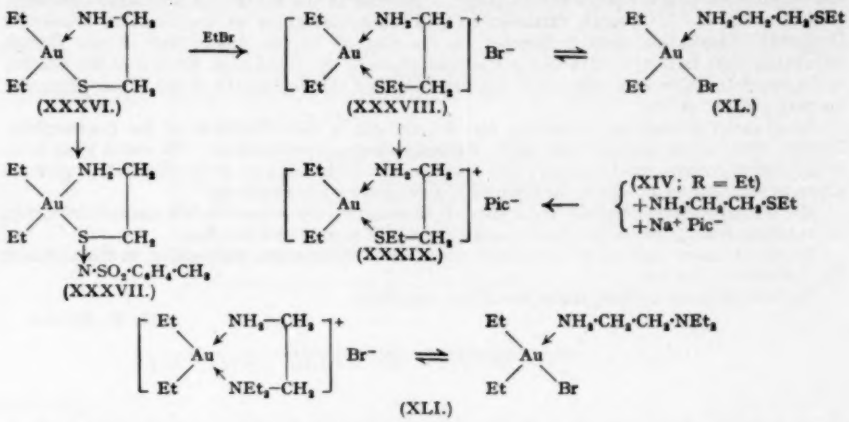


(XXXV.)

Every investigation which Gibson undertook in this field produced more evidence for the correctness of his main beliefs—that simple aurous and auric ions, Au^+ and Au^{+++}, cannot exist and that the gold atom, in either state of oxidation, must for stability acquire an additional covalent link, univalent gold thus becoming two-, and tervalent gold four-, covalent, and in the present account an attempt has been made to illustrate the diversity of the structural types which result.

No account of Gibson's work on gold would be complete without reference to his much prized process for the deposition of thin gold films on glass and other surfaces. The origin of the discovery is uncertain but it would have been surprising if, sooner or later, the action of alkali on an alcoholic solution of the dialkylgold halides had not been examined, though the resulting bright coherent " gold mirrors " which deposited on the walls of the vessels must have

astounded all who beheld them. Gibson spent several years of painstaking investigation in perfecting the process which in its final form consisted in exposing the surface to be gilded, after scrupulous cleaning, to a solution of diethylmonobromogold, calculated in amount to give the required film thickness, and sodium ethoxide in pure ethanol. Not only was it possible in this way to produce bright reflecting mirrors, which Gibson took great delight in presenting


Et NH₂–CH₂ Au Et S—CH₂ (XXXVI.)
EtBr
Et NH₂–CH₂ Au Et SEt–CH₂ (XXXVIII.) Br⁻
Et NH₂·CH₂·CH₂·SEt Au Et Br (XL.)
N·SO₂·C₆H₄·CH₃ (XXXVII.)
(XXXIX.) Pic⁻
(XIV; R = Et) +NH₂·CH₂·CH₂·SEt +Na⁺ Pic⁻
Et NH₂–CH₂ Au Et NEt₂–CH₂ Br⁻
Et NH₂·CH₂·CH₂·NEt₂ Au Et Br (XLI.)

to his friends, but also uniform transparent films so thin as to appear blue in transmitted light. The films were easily detached by rubbing and were floated off by water but, by a simple procedure discovered later, it was found possible to cover them with a thin protective layer of silica. So treated, they required no special care in handling and could even be submitted without damage to the lamination process employed in the manufacture of " safety glass." It is indeed unfortunate that Gibson never lived to bring his process to that state of commerical development upon which he had set such high hopes.

In the preparation of this notice I have been greatly assisted by Dr. M. P. Applebey, Dr. F. H. Brain, and Professor J. Read, F.R.S. Dr. Brain prepared the section dealing with the organic compounds of gold and Professor Read that on Professor Gibson's stereochemical investigations.

J. L. SIMONSEN.

DONALD CUMMING WILSON.

1898—1950.

THE untimely death of Donald Cumming Wilson on 4th September, 1950, while on holiday at Boat of Garten, Inverness-shire, has all too soon removed from a unique sphere of influence one of Edinburgh's best known personalities in the chemical profession.

" D. C.," as he was affectionately called by his friends, was born in Tranent, East Lothian, on 3rd January, 1898, and received his early schooling at the local Higher Grade School and later proceeded to Broughton Secondary School, Edinburgh. He entered the Heriot–Watt College in 1915 and studied under the late Professor A. A. Boon, completing his course for the College Associateship in Applied Chemistry and simultaneously graduating B.Sc. (Edin.) in 1919. He was elected a Fellow of the Royal Institute of Chemistry in 1944 and a Fellow of the Royal Society of Edinburgh in 1945.

On leaving the College he joined the staff of Messrs. T. & H. Smith as a Works Chemist, being chiefly concerned with the Opiates Department. He won steady promotion in the firm and in 1941 he became a Director and in 1946 he was appointed Managing Director.

Mr. Wilson took a keen interest in foreign trade connected with pharmaceutical raw materials and products. In recent years he had visited the U.S.A., Canada, India, Sweden, France, and Denmark in pursuance of his Company's interests in such matters. Immediately before his

death, he attended at Geneva as trade representative for Britain on the Commission on Narcotic Drugs held under the auspices of the Economic and Social Council of the United Nations Organisation.

Mr. Wilson's health was not always of the best, but at no time did he spare himself in the service of his firm or in connection with matters of public interest in which he engaged. He was a Governor of the Heriot–Watt College, a Director of the Edinburgh Merchant Company, a Member of the Edinburgh Chamber of Commerce, Chairman of the Scottish Wholesale Druggists' Association, and a Member of the Council of the Association of the British Pharmaceutical Industry. He was a Past-Chairman of the Edinburgh Section of the Society of Chemical Industry and was one of the forces behind the foundation of the Lister Memorial Lecture of that Society.

Apart from professional interests, Mr. Wilson was a Past-President of the Corstorphine Literary Association and an Elder in St. Ninian's Church, Corstorphine. He was a keen lover of his native county, East Lothian, and spent many of his holidays in the Scottish Highlands where he was able to indulge in his hobbies of photography and motoring.

Mr. Wilson endeared himself to all with whom he came into contact by his absolute integrity, his constant consideration for others, and his sense of justice and fairplay.

To the chemical and pharmaceutical professions in Edinburgh, his passing, in the prime of life, is indeed a sad loss.

Mr. Wilson is survived by his wife and two daughters.

H. B. NISBET.

THE CHEMICAL SOCIETY

ANNIVERSARY MEETINGS

Tuesday, March 20th, 1951.

4.00 p.m.	The Presidential Address, " Concepts in Catalysis—The Contributions of Paul Sabatier and Max Bodenstein."
6.30—8.30 p.m.	Reception and Conversazione in the Apartments of the Royal Society in Burlington House.

Wednesday, March 21st, 1951.

10.00 a.m.	Annual Meeting of Local Representatives.
11.30 a.m.	The One Hundred and Tenth Annual General Meeting.
12.15—4.00 p.m.	Visits to Research Establishments in the London area.
7.00 for 7.30 p.m.	The Anniversary Dinner.

Full particulars have been circulated to Fellows.

SCIENTIFIC MEETINGS DURING MARCH, 1951

LONDON.

Thursday, March 15th, 1951, at 7.30 p.m.

The following papers will be read and discussed:

" The Chloride Ethoxides of Zirconium." By D. C. Bradley, F. M. Abd-El Halim, and W. Wardlaw.

" The Structure of Olefin Compounds. Part II." By J. Chatt.

" High Temperature Chemistry of the System CaO–UO_2. The Ternary System Ca–U–O." By K. B. Alberman, R. S. Blakey, and J. S. Anderson.

ABERDEEN.

Thursday, March 22nd, 1951, at 7.30 p.m.

Lecture, **Chemistry in Relation to Soil Science,** by Dr. W. T. H. Williamson, F.R.I.C.

Joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry to be held in the Chemistry Department, Marischal College, Aberdeen.

BIRMINGHAM.

Friday, March 16th, 1951, at 4.30 p.m.

Lecture, **Some Recent Advances in the Chemistry of Fluorine Compounds,** by Professor H. J. Emeléus, D.Sc., F.R.S.

Joint meeting with the University Chemical Society to be held in the Chemistry Department of the University, Birmingham.

BRISTOL.

Thursday, March 1st, 1951, at 7 p.m.

Lecture, **Solid and Catalytic Reactions with Reference to the Practical Problems of Industry,** by Professor W. E. Garner, C.B.E., F.R.S.

Joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry to be held in the Chemistry Department, The University, Bristol.

Thursday, March 15th, 1951, at 7 p.m.

Lecture, **Recent Progress in the Study of Metal Oxidation and Corrosion,** by Dr. W. H. J. Vernon, O.B.E.

Joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry to be held in the Chemistry Department, The University, Bristol.

EDINBURGH.

Thursday, March 15th, 1951, at 7.30 p.m.

Lecture, **Some Observations on Materials of Construction for Chemical Plants,** by Dr. N. P. Inglis.

Joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry to be held in the North British Station Hotel, Edinburgh.

EXETER.

Saturday, March 10th, 1951, at 2.15 p.m.

Discussion, **Training of Scientists.**

Joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry to be held in the Washington Singer Laboratories, Prince of Wales Road, Exeter.

HULL.

Thursday, March 1st, 1951, at 8 p.m.

Official Meeting. Tilden Lecture, **Atoms and Radicals in Aqueous Solution,** by Professor F. S. Dainton, M.A., Ph.D.

To be given in the Science Lecture Theatre, University College, Hull.

IRISH REPUBLIC.

Friday, March 9th, 1951, at 8 p.m.

Lecture, **The Structure of Macrozamin,** by Dr. B. Lythgoe, M.A.

Joint meeting with the Werner Society to be held in the Department of Chemistry, Trinity College, Dublin.

Wednesday, March 14th, 1951, at 7.45 p.m.

Lecture, **The Production and Applications of Radioactive Isotopes,** by Mr. S. H. Bales, M.Sc., F.R.I.C.

Joint meeting with the Institute of Chemistry of Ireland to be held in the Department of Chemistry, University College, Dublin.

Wednesday, March 28th, 1951, at 7.45 p.m.

Lecture, **William Higgins (1763–1825),** by Professor T. S. Wheeler, D.Sc., F.R.I.C.

To be given in the Chemistry Department, University College, Dublin.

LIVERPOOL.

Thursday, March 8th, 1951, at 4.30 p.m.

Lecture, **Polyacetylenes,** by Professor E. R. H. Jones, D.Sc., F.R.S.

Joint meeting with the British Association of Chemists, the Royal Institute of Chemistry, and the Society of Chemical Industry to be held in the Chemistry Lecture Theatre, The University, Liverpool.

MANCHESTER.

Thursday, March 15th, 1951, at 10 a.m.—12.30 p.m., 2.30 p.m.—4.30 p.m., 5.30 p.m.

Symposium, **The Chemistry of Cell Division.**

Joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry to be held at the University, Manchester.

NEWCASTLE AND DURHAM.

Friday, March 2nd, 1951, at 5 p.m.

Meeting for the reading of original papers.

To be held in the Chemistry Building, King's College, Newcastle-on-Tyne.

NOTTINGHAM.

Cancellation of Meeting.

Thursday, March 8th, 1951.

The Lecture entitled "Starch Metabolism in the Higher Plants," which was to have been given by Professor S. Peat, has been postponed.

ST. ANDREWS AND DUNDEE.

Friday, March 2nd, 1951, at 5.15 p.m.

Lecture, **Analysis of Proteins and Amino-acids,** by Professor H. D. Springall, M.A., D.Phil.

To be given in the Chemistry Department, United College, St. Andrews.

SHEFFIELD.

Thursday, March 1st, 1951, at 5.30 p.m.

Lecture, **The Chemistry of Extractives from Hard Woods,** by Professor F. E. King, M.A., D.Phil.

Joint meeting with the University Chemical Society to be held in the Chemistry Lecture Theatre, The University, Sheffield.

SOUTH WALES.

Thursday, March 1st, 1951, at 6 p.m.

Lecture, **Some Naturally Occurring Derivatives of Tropolones,** by Professor A. R. Todd, D.Sc., F.R.S.

Joint meeting with University College Cardiff Chemical Society to be held at University College, Cardiff.

Friday, March 2nd, 1951, at 5.30 p.m.

Lecture, **Some Naturally Occurring Derivatives of Tropolones,** by Professor A. R. Todd, D.Sc., F.R.S.

Joint meeting with University College Swansea Chemical Society and the Royal Institute of Chemistry to be held at University College, Swansea.

Thursday, March 8th, 1951, at 6 p.m.

Lecture, **Some Aspects of Infra-red Measurements in Chemistry,** by Dr. H. W. Thompson, M.A., F.R.S.

Joint meeting with University College Cardiff Chemical Society to be held at University College, Cardiff.

PROCEEDINGS

OF THE

CHEMICAL SOCIETY

Minutes of a

SCIENTIFIC MEETING

held at Burlington House on Thursday, 18th January, 1951, at 7.30 p.m.

The President, PROFESSOR E. K. RIDEAL, M.B.E., M.A., D.Sc., F.R.S., was in the Chair.

MINUTES.

The Minutes of the Scientific Meeting held at Burlington House on December 14th, 1950, were read and were confirmed and signed.

VACANCIES ON COUNCIL 1951.

The list of Vacancies on Council due to be filled at the Annual General Meeting to be held on Wednesday, March 21st, 1951, was read.

FORMAL ADMISSION OF FELLOWS.

The following were admitted Fellows of the Society: John C. Lunt, I. W. Preston, N. S. Curtis, P. G. Wilkinson, B. E. Dawson, Nathan Fisher, O. H. Wheeler, A. Mathias, J. R. Heron, J. H. Mallows, H. C. Hornsey.

CENTENARY LECTURE.

The President called upon Professor Dr. K. Linderstrøm-Lang to deliver the Centenary Lecture entitled, "Structure and Enzymatic Breakdown of Proteins."

At the conclusion of the lecture a vote of thanks to the Lecturer, moved from the Chair, was carried with acclamation.

OFFICIAL ANNOUNCEMENTS.

DEATHS.

The Council regret to announce the deaths of the following Fellows:

	Elected.	Died.
Arthur George Vale Berry (Ellesmere Port)	Dec. 4th, 1919.	Sept. 1950
John William Cobb (Headingley) ...	June 20th, 1918.	Nov. 25th, 1950.
Thomas Rennie Cowie (Glasgow)	Dec. 7th, 1882.	Dec. 17th, 1950.
Harold Davenport (Scunthorpe)	Mar. 15th, 1945.	Aug. 1949.
Gerald Clifton Evans (Stratford-on-Avon)	Dec. 4th, 1919.	Dec. 1949.
John William Ingham (Edinburgh) ...	May 15th, 1941.	Jan. 12th, 1951.
John Trevor Nicholl (Belfast)	May 20th, 1926.	Dec. 24th, 1950.
James Frederick Spencer (Liverpool)	May 3rd, 1906.	Dec. 31st, 1950.
Frank Robert Stephens (N.W.1)	Dec. 5th, 1895.	Dec. 7th, 1950.

CONGRATULATIONS.

The President has conveyed the congratulations of the Society to Mr. Harold James Page (Trinidad) on the award of the C.M.G. gazetted in the New Year Honours List.

ELECTION OF NEW FELLOWS.

The following 72 candidates were elected Fellows of the Society on January 18th, 1951:

Morris Benjamin Berenbaum.
Peter John Russell Bourne.
Edna Brown.
Geoffrey Riggs Buckwalter.
Miljenko Buljan.
Graham John Bullen.
William George Burns.
Norman Henry Cromwell.
Michael William Davies.
Franklin Otto Davis.
John Edward Dove.
Allan Whineray Downs.
James Albert Farr, jun.
Charles Fox.
Kenneth Gaimster.
Emil John Geering.
Robert Aloysius Gilhooley.
Raymond George Gilson.
Frank Glockling.
John Tracey Greaves.
Albert Lawrence Green.
Gerald Ernest Green.
Ronald Henry Hackman.
Richard Edward Hands.
Bela Ann Hext.
John Allatt Hicks.
Rennie John Whalley Holt.
Paul William Howerton.
John Manson Hoyt.
Dillwyn John Jenkins.
Richard David Johnson.
Oswald Hilton Keys.
Cyril David Kopkin.
David Kritchevsky.
Gene Kritchevsky.
Lester Peter Kuhn.
Royston Ernest Walter Lake.
Edward Albert Lanham.
Arthur James Lindsey.
Peter Arthur Lockyer.
Donald Manson.
Giovanni Battista Marini-Bettolo.
Arthur Morgan.
Sister Marie Joannes O'Donnell.
Robert A. Odum.
Sydney Ogden.
Brian Michael Oliver.
Denis Pedder.
Karl Pfister.
Pierre Piganiol.
Michael David Potter.
John Karel Prall
James Peter Ringe.
William Henry Ritchie.
Bryan Mark Roberts.
Edward Francis Rogers.
Jean Sandiford.
Geoffrey Martin Saul.
Lawrence Neville Short.
Crispin John Stephen Moncreiff Simpson.
Hamish Small.
Garth John Smart.
Lee Anthony Subluskey.
Martyn Christian Raymond Symons.
Edwin Percival Taylor.
Derek Taylor.
Alfred Leslie Thomas.
Brian Russell Thomas.
David Henry Thomas.
Colin Frederick Timberlake.
Kenneth Robert Harry Wooldridge.
Gordon Youatt.

RESEARCH FUND.

A meeting of the Research Fund Committee will be held in May next.

Applications for Grants, to be made on forms obtainable from the General Secretary, must be received on or before May 1st, 1951. Applications from Fellows will receive prior consideration.

Attention is drawn to the fact that the income arising from the Donation of the Worshipful Company of Goldsmiths is principally devoted to the encouragement of research in Inorganic and Metallurgical Chemistry, and that the income from the Perkin Memorial Fund is to be applied to investigations relating to problems connected with the Coal Tar and Allied Industries.

SCIENTIFIC PUBLICATIONS GRANT-IN-AID.

The Society has received through the Royal Society a further grant of £2,000 towards the cost of publications from the Government Scientific Publications Grant-in-Aid.

GIFTS.

Acknowledgment is made of gifts of the Society's publications from Miss N. J. Broadway, Dr. A. F. Campbell, Mr. B. J. Moody, and Miss J. M. L. Stephen.

INTERNATIONAL NOMENCLATURE.

The Council has considered the general position with regard to international agreement on nomenclature and, in particular, the recommendations of the Commission of Nomen-

clature of Organic Chemistry of the International Union of Pure and Applied Chemistry as reported in the *Comptes rendus* of the 15th Conference held at Amsterdam in 1949.

The view was accepted by Council that international differences of nomenclature frequently form a real and serious barrier to the understanding of, and progress in, chemistry; that nomenclature, like grammar, has as its object the accurate and intelligible conveyance of information from one scientist to another; that no prestige or absolute value should attach to nomenclature apart from this object; and that, in consequence, conformity with internationally agreed nomenclature is most desirable even when the nomenclature so agreed may not seem to British chemists the best possible in particular cases.

It was decided that all feasible steps should be taken to foster international collaboration and to present British views for international consideration. Appreciation of the cordial and helpful co-operation displayed by the staff of *Chemical Abstracts* (U.S.A.) in lengthy correspondence with the Chemical Society's Editors was expressed.

The recommendations of the Organic Commission of the International Union were accepted for use in the Society's publications, except for a few specified points which the Commission would be requested to reconsider.

THE UNIT OF HEAT.

In response to a communication from the Royal Society it has been agreed that in the Chemical Society's publications expression of quantities of heat and all other dependent concepts in both joules and calories shall be encouraged.

EDITORIAL REPORT ON NOMENCLATURE.

The Indexes to the *Journal* for 1950 will include the first of a series of Editorial Reports on Nomenclature of which the following is the introduction:

> It is hoped to publish annually an Editorial Report on developments in nomenclature as practised in the Chemical Society's publications, to include broad questions of general principle and individual items of wide interest, but not matters of concern only in particular cases. In this, the first of such Reports, reliance has been placed on A. D. Mitchell's "British Chemical Nomenclature" (Edward Arnold, 1948) as giving standard British practice at the time of its publication (though the opinions expressed there on controversial matters have the weight of the author's long experience rather than of official rulings). The Reports will not necessarily be confined only to the previous twelve months; the present Report necessarily draws to some extent on earlier years to bridge the gap back to Dr. Mitchell's book, and it deals with matters of two types: (i) new decisions on nomenclature, and (ii) points of established nomenclature which warrant special mention.
>
> At the outset it will be well to make clear two principles. First, strict systematic nomenclature need not be used in the Society's publications when it obscures genetic principles discussed in a particular paper. Acceptable variants can usually be found, but in such cases the systematic name should also be given at least once (usually best in the Experimental section) so that searchers can locate the substance in indexes; however, a real warrant is required for such exceptions. Secondly, those who hope for an invariable nomenclature are doomed to disappointment; nomenclature must develop as chemistry develops, and its value is proportional to its flexibility, particularly when new ideas require expression.

Reprints of the report may be obtained from the General Secretary price one shilling, post free.

WORLD METALLURGICAL CONGRESS.

A World Metallurgical Congress will be held at Detroit, Michigan, on October 15th–19th, 1951, under the auspices of the American Society for Metals. Further details for intending participants in the Congress may be obtained from W. H. Eisenman, Secretary, American Society for Metals, 7301, Euclid Avenue, Cleveland 3, Ohio, U.S.A.

MEETINGS OUTSIDE LONDON

BIRMINGHAM.

" Homolytic Aromatic Substitution," by Professor D. H. Hey, D.Sc., F.R.I.C.

A joint meeting with the University Chemical Society was held in the Department of Chemistry of the University on December 8th, 1950, with Professor H. W. Melville in the Chair.

Aromatic substitution reactions involving free radicals and atoms were reviewed. Quantitative measurements now enabled tentative rules to be established for both orientation and activation (or deactivation) of the nucleus by substituent groups. In the light of existing knowledge all substituent groups are of the *ortho-para*-directing type and all show a positive activating effect on the nucleus, but such effects are less pronounced than those encountered in heterolytic substitution reactions. Quantum-mechanical interpretations of these results were discussed.

After an interesting discussion, a vote of thanks, proposed by Dr. E. J. Bourne, was carried with acclamation.

EDINBURGH.

" Modern Trends in Fuels and Lubricants," by Dr. E. M. Dodds.

A joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry was held in the North British Station Hotel on December 14th, 1950, with Professor S. J. Watson in the Chair.

After the discussion a vote of thanks to the Lecturer, moved by Professor Watson, was carried with acclamation.

" Some Problems in the Structure and Physical Properties of Industrial High Polymers," by Professor P. D. Ritchie, Ph.D.

A joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry was held in the North British Station Hotel on January 18th, 1951, with Dr. Neil Campbell in the Chair.

A discussion followed, and a vote of thanks, moved by Mr. F. J Bolton, was carried with enthusiasm.

LIST OF APPLICATIONS FOR FELLOWSHIP

(*Fellows wishing to lodge objection to the election of these candidates should communicate with the Honorary Secretaries within ten days of the date of publication of the* Journal *for February* 1951. *Such objections will be treated as confidential. The forms of application are available in the Library.*)

Anderson, Ronald James, B.Sc. (St. Andrews), A.R.I.C. British. 18, Parsons Green Terrace, Edinburgh 8. Research Chemist. *Signed by:* W. M. Ames, F. J. Bolton, R. R. A. Pride.

***Anderson, Robert Moffat,** B.Sc. (Dunelm). British. 10, Musgrave Road, Low Fell, Gateshead 9, Co. Durham. Research Student. *Signed by:* G. A. Swan, R. Raper, G. R. Clemo.

***Barron, Gordon,** B.Sc. (Lond.), A.R.I.C. British. 102, Hawarden Crescent, Sunderland. R.A.F. *Signed by:* J. H. Wilkinson, N. Ferry, J. Gibson.

***Bottle, Robert Thomas,** B.Sc. (Lond.). British. 24, Hunton Road, Erdington, Birmingham 23. Development Chemist, Dunlop Rubber Co., Ltd. *Signed by:* H. I. Stonehill, C. E. Kendall, W. H. Hogg.

***Brown, Christine Mavis,** B.Sc. (Glas.). British. 6, Killiegrew Road, Maxwell Park, Glasgow, S.1. Research Student. *Signed by:* S. J. Thomson, T. H. Goodwin, N. Grassie.

Brown, Desmond Goble, B.Sc. (N.Z.). British. 30, Chapman Street, Kaikorai, Dunedin, N.W.2, New Zealand. Student, Otago University. *Signed by:* F. G. Soper, A. D. Campbell, W. S. Fyfe.

***Brown, Joan Patricia,** B.Sc. (Lond.). British. 12, Woodfield Road, Ealing, W.5. Assistant Mistress, Notting Hill and Ealing High School. *Signed by:* J. W. E. Brading, A. G. Foster, T. G. Bonner, Gwyn Williams.

Buchanan, William Kerr, B.Sc. (Edin.), A.R.I.C. British. 34, Alexandra Place, Stirling. Chemist, The Distillers Co., Ltd., Menstrie. *Signed by:* W. G. Bennett, I. C. Willox, A. R. Chambers.

Bullough, William, B.Sc. (Lond.), A.R.I.C. British. The British Iron and Steel Research Association, Sketty Hall, Singleton Park, Swansea. Research Chemist. *Signed by:* F. W. Salt, E. E. Ayling, C. W. Shoppee, R. H. Davies.

Chisholm, Donald Strachan, B.Sc. (Glas.). British. 209, Auldhouse Road, Newlands, Glasgow, S.3. Industrial Chemist. *Signed by:* J. D. Loudon, C. Buchanan, T. H. Goodwin.

***Climie, Ian Ernest.** British. 21, Dochrane Street, Falkirk. Student, Edinburgh University. *Signed by:* Neil Campbell, D. Taylor, M. Ritchie.

***Clough, Edward Alfred,** B.Sc. (L'pool.). British. 5, Stevenson Crescent, St. Helens. Principal Assistant to Chief Analyst, Muren, Ltd. *Signed by:* A. S. Nickelson, F. Fairclough, F. P. Johnson.

Cohn, Peter, B.Sc. (Lond.), A.R.I.C., M.P.S. British. 112, Cardiff Road, Llandaff, Cardiff. Rockefeller Research Student, Whitchurch Hospital, Cardiff. *Signed by:* S. Thorburn, L. W. Tyrrell, A. A. Evans.

***Cole, Clifford Paul.** British. 162, Dukes Avenue, New Malden. Assistant Research Chemist. *Signed by:* R. N. Faulkner, D. R. Duncan, D. E. Eddowes.

***Coleby, Bryan,** B.Sc. (Dunelm). British. 50, Angerton Gardens, Fenham, Newcastle-on-Tyne, 5. Student. *Signed by:* G. A. Swan, G. R. Clemo, J. Weiss.

***Cooper, James Young,** B.Sc. (Aberd.), A.R.I.C. British. 5, Elmfield Avenue, Aberdeen. Research Student, Marischal College, Aberdeen. *Signed by:* R. M. Barrer, O. M. Meston, R. H. Thomson.

***Cooper, Sidney Alfred.** British. 153, Well Lane, Harden, Walsall. Chemical Laboratory Assistant. *Signed by:* F. R. Harris, E. J. Amies, W. R. Stanton.

***Corish, Patrick Joseph.** British. 13, St. David's Road, Port Talbot, Glamorgan. Serving in H.M. Forces (R.A.F.). *Signed by:* C. W. Shoppee, E. E. Ayling, B. G. Gowenlock.

***Cundall, Robert Bowser,** B.Sc. (St. Andrews). British. York Road, Barmby Moor, York. Research Student. *Signed by:* H. T. Openshaw, C. Horrex, John Read.

Davidson, Francis Stanley, B.A. (Cantab.). British. 22, Denewell Avenue, Low Fell, Co. Durham. Student, St. John's College, Cambridge. *Signed by:* F. G. Mann, P. Maitland, B. R. Brown.

Dunton, George Herbert, B.Sc. (Lond.). British. Brewery Laboratory, Whitbread and Co., Ltd., Chiswell Street, London, E.C.1. Chemist. *Signed by:* E. Barton-Wright, G. Harris, N. S. Curtis.

Earland, Christopher, M.Sc. and Ph.D. (Lond.), A.R.C.S., A.R.I.C. British. The Research Laboratory, Wolsey Ltd., Abbey Park Mills, Leicester. Chief Research Chemist. *Signed by:* Peter Alexander, K. A. Stacey, M. Fox.

***Ellis, Peter Manfrid,** B.Sc. (Lond.). British. Sutherland Tower, Higher Warberry Road, Torquay. Student. *Signed by:* L. H. Long, H. T. S. Britton, S. J. Gregg.

Fletcher, Alan Challoner, B.Sc. (L'pool.), A.R.I.C. British. 16, Shepley Close, Carshalton. Industrial Chemist, Vinyl Products Ltd. *Signed by:* H. Warson, J. R. Hickman, G. F. Reynolds.

Garratt, William Charles, B.Sc. (Lond.), F.R.I.C. British. 30, St. Wystans Road, Derby. Analytical Chemist, British Celanese Ltd. *Signed by:* W. Challis, M. H. Wilcox, W. Hunter, A. G. Catchpole.

Gordon, Maxwell, M.S. and Ph.D. (Penn.). American. 25, Phillimore Gardens, London, N.W.10. American Cancer Society, British-American Exchange Fellow, Imperial College of Science and Technology. *Signed by:* R. P. Linstead, H. N. Rydon, C. L. Leese.

***Huddleston, Patrick Robinson,** B.Sc. (Dunelm). British. 35, Endor Crescent, Burley-in-Wharfedale, Yorkshire. Research Student. *Signed by:* G. R. Clemo, R. Raper, G. A. Swan.

***Huggard, Arthur James,** B.Sc. (Birm.). British. 17, Rollason Road, Erdington, Birmingham 24. Research Student, Birmingham University. *Signed by:* M. Stacey, L. L. Bircumshaw, S. R. Carter.

***Hunter, Cornelius Newbold.** British. 6, Alton Gardens, Twickenham. Research Assistant, Paint Research Station. *Signed by:* D. R. Duncan, D. E. Eddowes, D. F. Rushman.

***Ingles, Thomas Alan,** B.Sc. (Birm.). British. 2, Dency Grove, High Lane, Tunstall, Stoke-on-Trent. Research Student. *Signed by:* M. Stacey, S. R. Carter, W. G. Overend.

***Jackson, Anthony Hugh.** British. 3, Foxley Road, Thornton Heath. Student, Christs' College, Cambridge. *Signed by:* A. W. Johnson, B. Lythgoe, F. G. Mann.

Judd, Gerard Forsyth, A.B. (Utah), M.S. (Portland). American. 210, Waldron Street, West Lafayette, Indiana, U.S.A. Research Fellow, Purdue University. *Signed by:* James H. Brewster, Nathan Kornblum, Herbert C. Brown.

***Kaufer, Otto Samuel,** B.S. (City College, N.Y.), M.S. (Polytechnic Institute of Brooklyn). American. Lyson Perrins Laboratory, South Parks Road, Oxford. Research Student. *Signed by:* W. A. Waters, H. M. E. Cardwell, B. Bannister.

King, Edward Louis, Ph.D. (Calif.). American. Department of Chemistry, University of Wisconsin, Madison, Wisconsin, U.S.A. Assistant Professor of Chemistry. *Signed by:* S. M. McElvain, A. L. Wilds, W. S. Johnson.

Kingston, Margaret Gwenllian, B.Sc. (Wales), A.R.I.C. British. 13, Hickman Road, Penarth. Chemist, British Resin Products Ltd. *Signed by:* E. M. Evans, J. J. Wilson, J. E. Whitney.

***Lakin, Terence Leonard John.** British. 38, Trinity Avenue, Bush Hill Park, Enfield. Assistant Chemist. *Signed by:* G. Harris, J. T. G. Johnson, E. Barton-Wright.

***Lambert, Edgar,** A.R.I.C. British. 40, Lancaster Road, Carnforth, Lancs. Production Chemist, British Schering Manufacturing Laboratories. *Signed by:* N. McFarlane, E. Booth, E. N. Abrahart.

Lewis, Ronald Douglas, B.A. (Cantab.). British. 37, St. Philip's Road, Cambridge. Research Student. *Signed by:* F. G. Mann, P. Maitland, G. W. Kenner.

Liddle, William Stewart, B.Sc. (St. Andrews), F.R.I.C. British. 275, Blackness Road, Dundee. Lecturer, Technical College, Dundee. *Signed by:* R. Roger, J. D. M. Ross, I. A. Smith.

***Llewelyn, Gwilym Ionwy Wyn,** B.Sc. (Wales). British. Erwr Delyn, Penygroes, Llanelly. Research Student, University College of North Wales, Bangor. *Signed by:* W. Rogie Angus, F. H. Newth, S. Peat.

McGillivray, Roy, B.Sc. (Glas.), A.R.I.C. British. 32, Cotswold Road, Sheffield 6. *Signed by:* R. D. Haworth, A. S. C. Lawrence, T. S. Stevens.

***Mackenzie, Norman,** B.Sc. (Aberd.), A.R.I.C. British. 51, Beaconsfield Place, Aberdeen. Research Student. *Signed by:* R. M. Barrer, A. M. Meston, R. B. Strathdee.

Moss, Archibald James Ernest. British. 27, Wimborne Avenue, Hayes, Middlesex. Manager and Technical Adviser, The Master Cleaners Ltd. and London Co-operative Society Ltd. *Signed by:* A. Greenwood, R. P. Wood, A. E. Parkes.

Mott, Owen Eldred, B.Sc. (Lond.), A.R.I.C. British. 18, Holcombe Road, Upton, Poole, Dorset. Assistant Chief Analyst, The British Drug Houses Ltd. *Signed by:* G. H. Osborn, J. G. A. Cobb, C. M. Lavender.

***Naylor, Arthur,** B.Sc. (Manc.). British. 15, North Terrace, Oxhill, Stanley, Co. Durham. Research Student, King's College, Newcastle-on-Tyne. *Signed by:* L. C. Dick, W. H. Beck, C. W. Humphrey.

Paddock, Norman Lovelace, B.A. (Cantab.). British. Emmanuel College, Cambridge. Research Student. *Signed by:* A. G. Sharpe, R. N. Haszeldine, H. J. Emeléus.

***Phillips, Thomas Rowland,** B.Sc. (Birm.). British. 23, Harrison's Road, Edgbaston, Birmingham 15. Research Student. *Signed by:* L. L. Bircumshaw, C. N. Turton, F. M. Tayler.

Ratner, Jack Louis. British. 27, Edgware Road, London, W.2. Dispenser-Registered Optician. *Signed by:* A. Fraser McIntosh, C. H. Maile, R. W. Brooke.

***Redgrove, Peter William.** British. Orchard End, Albion Road, Coombe Hill, Kingston-on-Thames. Laboratory Worker, Whiffen and Sons, Ltd. *Signed by:* J. T. W. Mann, E. Glynn, H. E. Glynn.

***Reed, Kenneth Gordon,** B.Sc. (Wales). British. Police Station, Defynock, Brecon. Research Student, University College of North Wales, Bangor. *Signed by:* W. Rogie Angus, S. Peat, F. Holmes.

Ritchie, Bruce, B.Sc. (Sydney). British. c/o Pyco Products Pty. Ltd., 576—578, Parramatta Road, Petersham, N.S.W., Australia. Industrial Chemist. *Signed by:* T. Iredale, S. J. Angyal, H. C. Freeman.

***Roberts, Peredur John Pennant,** B.Sc. (Wales). British. Manarfryn, Trefriw, Caerns. Research Student, University College of North Wales, Bangor. *Signed by:* W. Rogie Angus, W. J. Whelan, S. Peat.

***Robinson, Norman.** British. 34, George Street, Belper, Derby. Industrial Chemist. *Signed by:* A. G. Catchpole, J. Wood, N. Smith.

***Rowe, Thomas Gordon,** A.R.I.C. British. 58, Bruntsfield Gardens, Edinburgh, 10. Works Chemist. *Signed by:* H. B. Nisbet, A. Mackie, H. H. Campbell.

***Sidle, Alan.** British. 15, Woodlands Gardens, Walthamstow, E.17. Student. *Signed by:* H. Holness, R. A. Tingey, M. R. Porter.

***Silber, Maurice,** B.Sc. (Lond.), British. 22, Highfield Gardens, N.W.11. Research Chemist. *Signed by:* M. Sulzbacher, H. L. Feuchtwanger, S. J. Davis.

Skrimshire, Gerald Ernest Hamor, F.R.I.C. British. 19, Tenby Avenue, Kenton. Deputy Chemical Production Manager, The British Drug Houses Ltd. *Signed by:* W. D. Johnson, V. Petrow, E. J. Chappel.

***Smith, Geoffrey William.** British. Danish Bacon Co. Ltd., 9/13, Cowcross Street, W. Smithfield, E.C.1. Assistant to Chief Chemist. *Signed by:* D. G. Allen, W. H. Simmons, A. P. Davson.

***Soulal, Maurice John.** British. 56, Doneraile Street, Bishops Park, London, S.W.6. Student, Acton Technical College. *Signed by:* J. H. Skellon, W. Davey, E. G. Cowley.

Stallard, John Arthur, B.Sc. (Lond.). British. 53, Bailey Road, Leigh-on-Sea. Industrial Works Chemist. *Signed by:* W. D. Robertson, D. Ridge, J. Ratcliffe.

Steiner, Eric Hubert, B.Sc. (Lond.), F.R.I.C. British. 24, Lankers Drive, North Harrow. Chief Chemist, Danish Bacon Co. Ltd. *Signed by:* G. W. Ferguson, L. E. Campbell, A. M. Taylor.

***Sutherland, Kenneth Stanley.** British. 32, Rylandes Road, Selsdon, South Croydon. Student, Kings College, London. *Signed by:* S. H. Harper, E. K. Rideal, D. H. Hey.

Tietze, Hans Roderick, B.Sc. (Lond.). British. 177, Blandford Road, Efford, Plymouth. Research Student, Battersea Polytechnic. *Signed by:* F. R. Goss, J. E. Salmon, D. A. Everest.

***Toms, Ronald George,** B.Sc. (Lond.). British. 2, Cranmer Street, Long Eaton, Notts. Analytical Chemist, County Analysts Department, Derbyshire. *Signed by:* J. Markland, R. W. Sutton, H. J. Higgins, D. R. Bell.

***Tulip, Robert,** B.Sc. (Dunelm). British. 17, Glebe Road, Forest Hall, Newcastle-on-Tyne. Research Chemist, King's College, Newcastle-on-Tyne. *Signed by:* G. R. Clemo, R. Raper, D. Holden.

Walch, Adolphe Marie Alfred, B.Sc. (Lond.). Belgian. 112, Cambridge Street, London, S.W.1. Research Student, Battersea Polytechnic. *Signed by:* C. L. Arcus, A. Houston, F. R. Goss.

***Whalley, Leslie Albert.** British. 51, Brownedge Road, Lostock Hall, Preston. Student, Municipal Technical College, Burnley. *Signed by:* J. D. C. Worsnop, A. E. Wales, H. Hebden.

Whitmarsh, John Marshall, M.Sc. (Lond.), A.R.I.C. British. Boots Pure Drug Co., Ltd., Chemical Department, Island Street, Nottingham. Biochemist. *Signed by:* B. Garforth, J. S. Dunning, E. H. Harvey.

Woodcock, Ernest Roland. British. 5, Cambridge Terrace, Dover. Chief Chemist, The Parker Pen Co., Ltd. *Signed by:* R. H. H. Stanger, J. C. Mellersh, W. H. Woodcock.

UNDER SPECIAL PROVISION APPERTAINING TO CANDIDATES RESIDENT ABROAD.

Bluestein, Bernard Richard, M.S. and Ph.D. (Ill.). American. School of Chemistry, Rutgers University, New Brunswick, New Jersey, U.S.A. Research Associate. *Signed by:* J. F. Lane, M. A. Manganelli.

Brenner, Joseph, M.S. (New York). American. 64, Prospect Avenue, Hackensack, New Jersey, U.S.A. Graduate Assistant in Chemistry, New York University. *Signed by:* Kurt Mislow.

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"Indications of geometrical isomerism with 2 : 2'-azopyridine." By R. J. W. LE FÈVRE and C. V. WORTH.

"1-Nitromethyl*cyclo*hexanol." By G. A. R. KON.

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